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ANXIETY, SUBSTANCE USE, ADHERENCE TO TREATMENT AND LEVEL OF FUNCTIONING IN SPECIALIZED PSYCHIATRIC CARE PATIENTS

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ACADEMIC DISSERTATION

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to my father

ABSTRACT

Background and Objective: A high proportion of patients with mental disorders experience concurrent anxiety symptoms and substance misuse. Such co-occurrence impacts the course and outcome of principal psychiatric disorders, while substance use comorbidity also increases the risk of physical morbidity and suicide. This is especially true for patients in specialized psychiatric care suffering from the most severe form of illness. Because of methodological variations in the studies on anxiety and substance use comorbidity, it remains unclear whether such conditions share similar characteristics across schizophrenia spectrum and mood disorders. Another prominent problem, contributing to unfavorable outcome and increased costs of mental disorders, is poor adherence to psychiatric treatment. While the majority of related studies focus on medical adherence, this study also investigates self-reported adherence to outpatient visits in specialized care psychiatric patients. As a consequence of severe course and poor treatment adherence, mental disorders are highly disabling. Subjective and objective functioning and ability to work, their interrelationships, and associated factors were investigated in this study.

Materials and Methods: The Helsinki University Psychiatric Consortium Study was performed as a cross-sectional study in the metropolitan area of Helsinki between 12.01.2011 and 20.12.2012, covering 10 community mental health centres, 24 psychiatric inpatient units, one day-care hospital, and two supported housing units. Patients aged between 18 and 64 years were selected based on stratified sampling, and all subjects provided an informed consent. Of the total of 1361 eligible patients, 447 completed the survey, yielding a participation rate of 33%, with a predominance of females (n=263, 65.8%). Patients were mainly middle-aged (mean 42.0 years, SD 13.0), and 90 (22.5%) were inpatients. Clinical diagnoses were collected from medical records and verified by the authors. For this study, patients were divided into three subgroups: schizophrenia or schizoaffective disorder (SSA, n=113), bipolar disorder (BD, n=99), and depressive disorder (DD, n=188). Anxiety symptoms were measured with the self-report Overall Anxiety Severity and Impairment Scale (OASIS); substance use was assessed with recorded substance use disorder diagnoses, Alcohol Use Disorders Identification Test (AUDIT), and original questionnaires; treatment adherence was assessed with patients´ self-reports; subjective level of functioning was assessed with the self-report Sheehan Disability Scale (SDS); and data on objective work status were gathered from medical records.

Results: Nearly half of all patients felt severe or extreme anxiety frequently or constantly. SSA patients experienced anxiety and avoided anxiety-provoking situations significantly less often than did patients with mood disorders. High neuroticism, symptoms of depression and borderline personality disorder, and low self-efficacy were associated with co-occurring anxiety within all diagnostic groups. Almost half of the patients reported hazardous alcohol use or were daily smokers. One-fourth of the patients had diagnoses of substance use disorders. Symptoms of anxiety and borderline personality disorder and low conscientiousness were associated with self-reported alcohol consumption. The majority of patients reported regular use of psychiatric medication (79.2%) and attending outpatient visits (78.5%). Outpatients were significantly more adherent than current inpatients. Non-adherence to outpatient visits was strongly associated with hospital setting and substance use disorder. Nearly one-third of mood disorder patients were employed, while in SSA patients this proportion was only 5.3%. Being outside the labour force was associated with number of hospitalizations, and perceived functional impairment and work disability were associated with current depressive symptoms.

Conclusions: In patients with mood or schizophrenia spectrum disorders, comorbid anxiety symptoms and hazardous substance use are common, interrelated, and accompanied by symptoms of borderline personality disorder and personality traits. Regardless of principal diagnosis, self-reported non-adherence to outpatient care is associated with hospital setting and substance use disorders. Severe course of disease and current depressive symptoms are likely to affect work status and perceived functional impairment, respectively. Thus, prevention, careful detection, and treatment of harmful substance use and co-occurring affective symptoms are necessary to enhance treatment adherence, and, eventually, functional level of patients with mood or schizophrenia spectrum disorders.

TIIVISTELMÄ

Tausta ja tavoitteet: Ahdistusoireet ja päihteiden ongelmakäyttö ovat yleisiä mielenterveyspotilailla ja vaikeuttavat taudinkulkua ja ennustetta. Samanaikainen päihteidenkäyttö on myös yhteydessä lisääntyneeseen somaattiseen sairastuvuuteen ja itsemurhariskiin. Nämä ongelmat korostuvat yleensä vaikeimmista ja vaikeahoitoisimmista mielenterveydenhäiriöistä kärsivillä psykiatrian erikoissairaanhoidon potilailla. Mielenterveydenhäiriöistä kärsivien potilaiden ahdistusoireita ja päihteidenkäyttöä käsittelevät tutkimukset ovat menetelmiltään vaihtelevia. Toistaiseksi epäselvää on, eroavatko ahdistusoireiden ja päihteiden ongelmakäytön taustatekijät mieliala- ja skitsofreniaryhmän häiriöistä kärsivillä potilailla.
Puutteellinen hoitoon sitoutuminen on merkittävä ongelma, jolla on kielteisiä vaikutuksia taudin ennusteeseen ja hoitokustannuksiin. Suurin osa hoitoon sitoutumista koskevista tutkimuksista keskittyy lähinnä sitoutumiseen lääkehoitoon, mutta toteutumattomilla suunnitelluilla avohoitokäynneillä on myös kielteisiä vaikutuksia hoidon tuloksiin ja edelleen työ- ja toimintakykyyn. Tässä tutkimuksessa lääkehoitoon sitoutumisen lisäksi selvitettiin myös avohoitokäynteihin sitoutumista. Tutkimuksessa arvioitiin sekä potilaiden omakohtaisia käsityksiä toiminta- ja työkyvystään, että sairauslomalla oloa ja työkyvyttömyyttä, sekä näiden keskinäisiä suhteita ja taustatekijöitä.

Aineisto ja menetelmät: Helsinki University Psychiatric Consortium Study toteutettiin poikkileikkaustutkimuksena pääkaupunkiseudulla 12.01.2011 – 20.12.2012 välisenä aikana 10:llä psykiatrian poliklinikalla, 24:llä psykiatrian osastolla, yhdellä psykiatrian päiväosastolla ja kahdessa tuetussa asumisyksikössä. Yhteensä 1361 potilaista, 447 ovat palauttaneet kyselyn, joten osallistumisprosentti oli 33%. Niistä potilaista 263 (65.8%) oli naisia. Potilaat olivat pääosin keski-ikäsiä (keski-arvo 42.0, keski-hajonta 13.0) ja 90 potilasta (22.5%) olivat osasoilta. Kliiniset diagnoosit perustuivat sairauskertomuksiin ja tarkistettiin tekijöiden toimesta. Potilaat jakautuivat päädiagnoosinsa mukaan kolmeen ryhmään: skitsofrenia tai skitsoaffektiivinen häiriö (SSA, n=113), kaksisuuntainen mielialahäiriö (BD, n=99) ja depressio (DD, n=188). Ahdistusoireita arvioitiin Overall Anxiety Severity and Impairment Scale (OASIS) itsearviointikyselyllä; päihteidenkäyttöä sairauskertomusten päihdehäiriödiagnooseja tutkimalla ja Alcohol Use Disorders Identification Test – kyselyllä (AUDIT). Sitoutumista hoitoon arvioitiin potilaiden kyselyllä. Subjektiivista toimintakykyä arvioitiin Sheehan Disability Scale – itsearviointikyselyllä (SDS) ja tieto ajankohtaisesta työkyvystä kerättiin sairauskertomuksesta.

Tulokset: Noin puolet potilaista oli kärsinyt vakavasta ahdistuksesta. SSA-ryhmän potilaat kokivat ahdistusta vähemmän ja välttivät ahdistavia tilanteita harvemmin kuin mielialahäiriöpotilaat. Ahdistus liitännäisoireena oli yhteydessä korkeaan neuroottisuuteen, masennusoireisiin ja tunne-elämältään epävakaan persoonallisuuden piirteisiin sekä heikkoon minäpystyvyyteen. Noin puolet potilaista raportoi haitallista alkoholinkäyttöä tai päivittäistä tupakointia. Neljäsosalla potilaista oli diagnosoitu päihteiden haitallinen käyttö tai päihderiippuvuus. Käytetyn alkoholin määrä oli suorassa yhteydessä ahdistusoireisiin ja tunne-elämältään epävakaan persoonallisuuden piirteisiin sekä luonteenpiirteistä alhaiseen tunnollisuuteen. Enemmistö potilaista raportoi säännöllisesti käyttäneensä psyykenlääkkeitä (79.2%) ja käyneensä avohoitokäynneillä (78.5%). Sitoutuminen avohoitoon oli vahvempaa avohoitopotilailla kuin osastohoidossa olevilla potilailla. Hoitoon sitoutumattomuus oli yhteydessä ajankohtaiseen sairaalahoitojaksoon ja päihdehäiriöön. Noin kolmasosa mielialahäiriöpotilaista oli työelämässä, kun taas vain 5.3% SSA-ryhmän potilaista kävi työssä. Työttömyys oli yhteydessä sairaalahoitojaksojen lukumäärään ja koettu toiminta- ja työkyvyttömyys ajankohtaisiin masennusoireisiin.

Loppupäätelmät: Ahdistusoireet ja päihteiden ongelmakäyttö ovat yhteydessä toisiinsa ja ovat yleisiä kaikissa kolmessa tutkitussa potilasryhmässä. Ahdistusoireet ja päihteidenkäyttö yhdistyivät tunne-elämältään epävakaan persoonallisuuden piirteisiin sekä luonteenpiirteistä neuroottisuuteen ja tunnollisuuteen. Potilaiden avohoitoon sitoutumattomuus oli yhteydessä ajankohtaiseen sairaalahoitoon ja päihdeongelmaan. Vaikeampi taudinkulku todennäköisesti alentaa työkykyä ja ajankohtaiset masennusoireet liittyvät koettuun toimintakyvyttömyyteen. Ahdistusoireiden ja päihdeongelmien huolellinen tunnistaminen ja asianmukainen hoito ovat tärkeitä sekä hoitoon sitoutumisen vahvistamiseksi, että potilaiden toiminta- ja työkyvyn parantamiseksi.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:

I. Karpov, B., Joffe, G., Aaltonen, K., Suvisaari, J., Baryshnikov, I., Näätänen, P., Koivisto, M., Melartin, T., Oksanen, J., Suominen, K., Heikkinen, M., Paunio, T., Isometsä, E., 2016. Anxiety symptoms in major mood and schizophrenia spectrum disorders. Eur Psychiatry. 37:1-7.

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ABBREVIATIONS

ANOVA – Analysis of variance

AUDIT – Alcohol Use Disorders Identification Test

BD – Bipolar disorder

BDI – Beck Depression Inventory

DD – Depressive disorder

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th edition

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition

ECR-R – Experiences in Close Relationships, Revised

GSE – General Self-Efficacy scale

HUPC – Helsinki University Psychiatric Consortium

ICD-10-DCR – International Classification of Diseases, 10th revision, Diagnostic Criteria for Research

MSI – McLean Screening Instrument for Borderline Personality Disorder

OASIS – Overall Anxiety Severity and Impairment Scale

PRISM – Psychiatric Research Interview for Substance and Mental Disorders

S5 – Short Five

SAD – Schizoaffective disorder

SDS – Sheehan Disability Scale

SSA – Schizophrenia or schizoaffective disorder

SUD – Substance Use Disorder

TADS – Trauma and Distress Scale

WHO – World Health Organization

1 INTRODUCTION

Common mental disorders, such as schizophrenia spectrum, mood, and anxiety disorders, are among the leading causes of the global burden of diseases, with increasing contributions to disability (Alonso et al., 2011; Wittchen et al., 2011; Vos et al., 2016). Of these disorders, anxiety disorders are most prevalent in the general population, also often emerging among psychiatric patients (Kessler et al., 2005b; Pirkola et al., 2005; Achim et al., 2011; Pavlova et al., 2015). Substance use disorders (SUDs) are also highly prevalent and co-occur with other mental disorders (Weaver et al., 2003; Grant et al., 2015; Lai et al., 2015). Both comorbid anxiety disorders and comorbid SUD worsen the course and outcome of principal mental disorders (El-Mallakh & Hollifield, 2008; Braga et al., 2013; Nesvåg et al., 2015) and contribute to early mortality by increasing physical morbidity and suicidal behaviour (Saarni et al., 2007; Wahlbeck et al., 2011; Frash et al., 2013; Yuodelis-Flores & Ries, 2015).

The phenomenon of comorbidity of mental disorders is well-known, whereas the aetiological and pathophysiological mechanisms remain obscure. Recent large genetic studies have demonstrated a mutual genetic basis for heterogeneous psychiatric disorders (e.g. schizophrenia, bipolar disorder, depression, autism spectrum disorders) (Smoller et al., 2013; Wray et al., 2013). Furthermore, anxiety and mood disorders are likely to form a cluster of internalizing disorders (Krueger, 1999), sharing genetic and psychopathological (e.g. high neuroticism) features (Hettema, 2008; de Moor et al., 2015). In addition, comorbidity of anxiety and mood disorders is associated with traumatic experiences (Hovens et al., 2012), low self-efficacy (De Las Cuevas et al., 2014), and borderline personality disorder (Zanarini et al., 1998; Mantere et al., 2006). Several studies have demonstrated that aetiology and course of schizophrenia spectrum disorders have similar risk factors (Van Os & Jones, 2001; Bahorik & Eack, 2010; Kurtz et al., 2013; Larsson et al., 2013). Analogously to anxiety disorders, SUDs are strongly related to various personality traits, symptoms of anxiety, depression, and borderline personality, as well as to early traumatic experience (Khan et al., 2005; Holma et al., 2013; Few et al., 2014; Zvolensky et al., 2015; Kristjansson et al., 2016).

However, it remains unclear whether factors responsible for comorbidity of mood and anxiety disorders also underlie covariation of anxiety symptoms and whether the same factors are associated with SUD comorbidity and co-incidence of anxiety symptoms in both schizophrenia spectrum and mood

disorders. Moreover, the role of putative risk factors in specialized psychiatric care patients (i.e. patients with the most severe course of illness) remains to be elucidated.

The burden of mental disorders results not only from the severity of these disorders, but also from poor adherence to psychiatric and somatic treatment, often emerging in patients with schizophrenia spectrum or mood disorders (Svarstad et al., 2001; Gilmer et al., 2004). Treatment adherence is a complex matter, impacted by various disease-, patient-, clinician-, and health care system-related factors (Jin et al., 2008; Joosten et al., 2008). Of these factors, severe course of the principal disorder, substance use comorbidity, and co-occurring affective and personality symptoms affect non-adherence to medication and outpatient care similarly in schizophrenia spectrum, bipolar, and depressive disorders (Coodin et al., 2004; Holma et al., 2010; Gibson et al., 2013; Leclerc et al., 2013; Czobor et al., 2015; Arvilommi et al., 2014). The major methodological challenge in adherence-related studies arises from variations in the definition of "adherence". Although it is explicated as concordance of patient´s behaviour with different instructions of a health care professional, most studies focus only on adherence to pharmacological treatment, paying much less attention to other treatment forms (e.g. psychosocial treatment, overall outpatient care). Thus, a comprehensive view of treatment adherence as a multi-factorial phenomenon is still deficient. Moreover, scarce studies investigate adherence simultaneously among in- and outpatients with schizophrenia spectrum or mood disorders.

Overall, more detailed understanding of characteristics of comorbidity and adherence to psychiatric treatment in different mental disorders will likely enable more effective targeting of treatment and rehabilitation, eventually mitigating the burden of psychiatric diseases. The dimensional and trans-diagnostic approach of such studies could be beneficial in addressing phenomenological similarity among heterogeneous psychopathology, thus, influencing treatment processes and the structure of health care.

2 REVIEW OF THE LITERATURE

2.1 DEFINITION AND DIAGNOSTIC CLASSIFICATION OF MENTAL DISORDERS

2.1.1 SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

Schizophrenia (or initially dementia praecox) was considered an autonomous mental disorder for over a century. However, due to growing clinical, genetic, and neuroimaging data, the conceptualization and definition of schizophrenia have changed over time (Tandon et al., 2013).

The current classification systems (ICD-10, DSM-IV, and DSM-5) are generally similar, especially in terms of core symptoms, with, however, some specific features. For instance, these classifications have a different time frame of symptoms, as ICD-10 requires presentation of the symptoms for one month, while this period in DSM-IV and DSM-5 is extended to 6 months. Unlike ICD, DSM includes the criterion of symptom-related functional impairment.

The criteria of DSM-IV and DSM-5 have no marked differences. DSM-5 clarifies that at least one of the characteristic symptoms of group A should be delusions, hallucinations, or disorganized speech. Also, DSM-5 no longer differentiates the subtypes of schizophrenia, as opposed to ICD-10 and DSM-IV.

The diagnostic criteria of schizophrenia are listed in **Table 1**.

The conceptualization of **schizoaffective disorder** remained challenging for decades. Whether initially characterized as a subtype of schizophrenia (DSM) or formulated as affective psychosis (ICD), schizoaffective disorder was distinguished from other psychotic disorders only in DSM-III (1980) and was named as such in ICD-10 (1992). Such cautious definitions probably result from weak reliability of the diagnoses (Maj et al., 2000; Jager et al., 2011) and ongoing debates about whether schizoaffective disorder represents a distinct class of psychopathology or a variant of schizophrenia or psychotic mood disorders (Cheniaux et al., 2008). Findings of substantial and overlapping heritability (Cardno et al., 2002) suggest that schizoaffective disorder is in the middle of a continuum of mental disorders, with the extremities being bipolar disorder and schizophrenia.

ICD-10 diagnosis of schizoaffective disorder requires the criteria of affective disorders (depression, mania, hypomania, mixed state) and the syndromal criteria of schizophrenia within the same episode of the disorder and concurrently for at least some time of the episode. Contrary to ICD-10, the DSM-IV and DSM-5 that during the same period of illness psychotic symptoms should be presented for at least 2 weeks in the absence of prominent mood symptoms. DSM-IV and DSM-5 specifies bipolar and depressive types, and ICD-10 the manic, depressive, and mixed types of schizoaffective disorder.

2.1.2 BIPOLAR DISORDER

Bipolar disorder is a chronic disorder characterized by recurrent fluctuations in mood state. The fluctuation in mood state comprises episodes of hypomania, mania, depression, or mixed states. Changes in mood profile are essential for diagnostics of bipolar disorders, requiring the presence of both hypomania/mania and depression at least once over a lifetime.

ICD-10, DSM-IV, and DSM-5 largely concur regarding the criteria of hypomania and mania. DSM differentiates bipolar type I (presence of depression and mania) and bipolar type 2 (presence of depression and hypomania), while ICD classifies the course of type 2 as 'other bipolar disorder'. In addition to the exclusion criteria of presence of psychoactive substance use or organic mental disorder, seen in both ICD and DSM, DSM also excludes hypomanic- or manic-like states induced by somatic antidepressant treatment (medication, electroconvulsive therapy, and light therapy). In terms of severity and functional disturbance, DSM hypomania state is characterized by symptoms not severe enough to cause marked impairment in social or occupational functioning, while manic state criteria do require such level of impairment, or need of hospitalization to prevent harm to self or others, or in the presence of psychotic features.

The symptoms of hypomania and mania are listed in **Table 2**. For criteria of depression, see **Table 3.**

Table 1. Diagnostic criteria for schizophrenia

ICD-10-DCR	DSM-IV and DSM-5
I. Either at least one of the symptoms listed under (1) or at least two of the symptoms listed under (2) should be present for most of the time during an episode of psychotic illness lasting for at least one month: (1) a. Thought echo, thought insertion or withdrawal, or thought broadcasting. b. Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception. c. Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body. d. Persistent delusions of other kinds that are culturally inappropriate and completely impossible **OR**	**I.** Two (or more)* of the following, each present for a significant portion of time during a one-month period (or less if successfully treated): [1] Delusions [2] Hallucinations [3] Disorganized speech (e.g. frequent derailment or incoherence) [4] Disorganized or catatonic behaviour [5] Negative symptoms, i.e. affective flattening, alogia (poverty of speech), or avolition (lack of motivation) * in DSM-IV, only one symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.
	II. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
(2) e. Persistent hallucinations in any modality, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas. f. Neologisms, breaks, or interpolations in the train of thought, resulting in incoherent or irrelevant speech. g. Catatonic behaviour such as excitement, posturing or waxy flexibility, negativism, mutism, and stupor. h. "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses	**III.** Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least one month of symptoms (or less if successfully treated) that meet Criterion I and may include periods of prodromal (symptomatic of the onset) or residual symptoms. During these prodromal or residual periods the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion I present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences).
II. If the patient also meets criteria for manic episode or depressive episode, the criteria listed under **I (1), (2)** above must have been met before the disturbance of mood developed.	**IV.** Schizoaffective Disorder and Mood Disorder with Psychotic Features (depressive or bipolar) have been ruled out because either: [1] No Major Depressive Episode, Manic Episode, or Mixed Episode have occurred concurrently with the active-phase symptoms; or [2] If mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
III. The disorder is not attributable to organic brain disease or to alcohol- or drug-related intoxication, dependence or withdrawal.	**V.** The disturbance is not attributable to physiological effects of a substance (drug of abuse, a medication) or a general medical condition.

ICD-10-DCR – International Classification of Disease, 10th revision, Diagnostic Criteria for Research; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

Table 2. Diagnostic criteria for hypomania and mania

ICD-10-DCR	DSM-IV and DSM-5
Hypomania A. The mood is elevated or irritable to a degree that is definitely abnormal for the individual concerned. B. ≥3 of the following with some interference with personal functioning in daily living: 1. Increased activity or physical restlessness 2. Increased talkativeness 3. Difficulty in concentration or distractibility 4. Decreased need for sleep 5. Increased sexual energy 6. Mild spending sprees, or other types of reckless or irresponsible behaviour, increased sociability or over-familiarity	**Hypomania** A. A distinct period of persistently elevated, expansive, or irritable mood, lasting for at least 4 days, that is clearly different from the usual non-depressed mood. B.≥3 of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree and are observable by others. 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep 3. More talkative than usual or pressure to keep talking 4. Flight of ideas 5. Distractibility 6. Increase in goal-directed or psychomotor agitation 7. Excessive involvement in pleasurable activities that have a high potential for painful consequences
Mania without psychotic symptoms A. A mood that is predominantly elevated, expansive, or irritable and definitely abnormal for the individual concerned. This mood change must be prominent and sustained for at least a week B. ≥3 of the following must be present (four if the mood is merely irritable), leading to severe interference with personal functioning in daily living 1. Increased activity or physical restlessness; 2. Increased talkativeness ('pressure of speech'); 3. Flight of ideas or the subjective experience of thoughts racing; 4. Loss of normal social inhibitions resulting in behaviour that is inappropriate to the circumstances; 5. Decreased need for sleep; 6. Inflated self-esteem or grandiosity; 7. Distractibility or constant changes in activity or plans; 8. Behaviour that is foolhardy or reckless and with risks the subject does not recognize, e.g. spending sprees, foolish enterprises, reckless driving; 9. Marked sexual energy or sexual indiscretions.	**Mania** A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary) B. ≥3 of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep (e.g. feels rested after only three hours of sleep) 3. More talkative than usual or pressure to keep talking 4. Flight of ideas or subjective experience that thoughts are racing 5. Distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli) 6. Increase in goal-directed activity (socially, at work or school, or sexually) or psychomotor agitation 7. Excessive involvement in pleasurable activities that have a high potential for painful consequences
Mania with psychotic symptoms The episode meets the criteria for mania without psychotic symptoms with also presence of: Delusions or hallucinations, other than those that are completely impossible or culturally inappropriate and hallucinations, that are not in the third person or giving a running commentary.	

ICD-10-DCR – International Classification of Disease, 10th revision, Diagnostic Criteria for Research; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th edition

2.1.3 DEPRESSIVE DISORDER

Depression is a mental disorder characterized by enduring low mood, accompanied by loss of interest in normally enjoyable activities, reduced energy and self-esteem, and often suicidal thoughts and intentions.

For the diagnostic criteria of depressive disorder, see **Table 3**.

ICD-10, DSM-IV, and DSM-5 are similar in terms of depressive symptoms and their time frame. DSM emphasizes depression-related functional impairment, while ICD only mentions that thestate of depressed mood is clearly abnormal for the individual. ICD differentiates four grades of severity: mild, moderate, and severe with or without psychotic symptoms. In turn, DSM-IV and DSM-5 have a set of diagnostic specifiers of severity (mild, moderate, severe, with or without psychotic symptoms) and course of disease (single or recurrent episode, in partial or full remission). In addition, in the section of syndromal specifiers, DSM-5 distinguishes depression with mixed features (when depression is accorded by subthreshold mania/hypomania) and depression with anxious distress.

Unlike DSM-IV, DSM-5´s section of mood disorders includes Disruptive Mood Dysregulation Disorder (chronic, severe persistent irritability) and Premenstrual Dysphoric Disorder.

2.1.4 ANXIETY DISORDERS

Anxiety is a natural emotion, the core feature of which is a subjectively unpleasant feeling of upcoming threat. Anxiety is characterized by a state of apprehension, various somatic symptoms, and behavioural changes. When anxiety becomes intensive or recurrent, impairing an individual`s psychosocial functioning, anxiety symptoms are conceptualized as anxiety disorders. The spectrum of anxiety disorders is relatively large, with various disorder-specific symptoms. However, the most common feature for all disorders is a feeling of worry and symptoms of panic induced by exposure to some anxiety-provoking situation or as a consequence of anxiety-provoking thoughts or beliefs.

Panic attack is an abruptly starting episode of intense fear or discomfort, including numerous somatic symptoms (e.g. accelerated heart rate, sweating, dry mouth, difficulty breathing, chest pain, nausea) and feelings of losing control, derealization, depersonalization, or fear of dying.

Table 3. Diagnostic criteria of depressive disorder.

ICD-10-DCR	DSM-IV and DSM-5
A. ≥2 of the following symptoms must be present for at least 2 weeks: [1] depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day [2] loss of interest or pleasure in activities that are normally pleasurable [3] decreased energy or increased fatigability. B. ≥2 of the following: [4] loss of confidence and self-esteem [5] unreasonable feelings of self-reproach or excessive and inappropriate guilt [6] recurrent thoughts of death or suicide, or any suicidal behaviour [7] complaints or evidence of diminished ability to think or concentrate such as indecisiveness or vacillation [8] change in psychomotor activity, with agitation or retardation (either subjective or objective) [9] sleep disturbance of any type [10] change in appetite (decrease or increase) with corresponding weight change	A. ≥5 of the following symptoms have been present during 2-week period and represent a change from previous functioning (at least one of the symptoms is either 1 or 2): [1] depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. [2] markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day [3] significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day. [4] insomnia or hypersomnia nearly every day [5] psychomotor agitation or retardation nearly every day [6] fatigue or loss of energy nearly every day [7] feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day [8] diminished ability to think or concentrate, or indecisiveness, nearly every day [9] recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

ICD-10-DCR – International Classification of Disease, 10th revision, Diagnostic Criteria for Research; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th edition

As indicated in **Table 4**, ICD-10-DCR, DSM IV, and DSM-5 include broadly the same classes of anxiety disorders with only slight differences. The section of anxiety disorders in DSM-IV includes Obsessive-compulsive disorder, Acute Stress Disorder, and Post-Traumatic Stress Disorder, while in ICD-10-DCR and DSM-5 these form distinct sections.

Table 4. Content of Anxiety Disorders section.

ICD-10-DCR, DSM-IV, DSM-5	Agoraphobia (in ICD-10 with or without panic disorder), Panic Disorder (in DSM-IV with or without agoraphobia), Social Phobia, Specific Phobia, Generalized Anxiety Disorder
DSM-IV, DSM-5	Substance/Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition
Only ICD-10-DCR	Mixed Anxiety and Depressive Disorder
Only DSM-IV	Obsessive-compulsive disorder, Post-traumatic Stress Disorder, Acute Stress Disorder
Only DSM-5	Separation Anxiety Disorder, Selective Mutism

ICD-10-DCR – International Classification of Disease, 10th revision, Diagnostic Criteria for Research; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th edition

2.1.5 SUBSTANCE USE DISORDERS

Substance use disorder is a condition in which use of one (or many) substance causes severe health consequences and results in significant impairment or distress. ICD-10-DCR, DSM-IV, and DSM-5 include the following substances: alcohol, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, and nicotine. DSM includes also caffeine-related disorders. The terminology related to substance use is a topic of debate. For instance, both ICD-10 and DSM-IV differentiate **substance abuse** (harmful use) and **dependence**, whereas in DSM-5 these terms are replaced with substance use disorder (combining the diagnostic criteria for both). Moreover, DSM-5 emphasizes omission of the term **addiction** from the current classification because of its uncertainty and negative connotation.

Dependence refers to repeated use of a substance(s), which results in difficulties in controlling its use, and persisting in its use despite harmful consequences, and which causes specific physical symptoms (withdrawal) upon cessation.

Abuse, in turn, refers to use of substance(s) in a way that clearly deviates from approved social or medical patterns, leading to physical harm.

Table 5 presents the diagnostic criteria of SUD.

Table 5. Diagnostic criteria of Substance Use Disorder.

ICD-10-DCR	DSM-IV	DSM-5
Substance Harmful Use	Substance Abuse (≥3 of the following within 12-month period):	Substance Use Disorder (≥2 of the following within 12-month period):
1. Substance use is responsible for physical or psychological harm, including impaired judgement or dysfunctional behaviour. 2. The nature of the harm is clearly identifiable. 3. The pattern of use has persisted for at least one month or has occurred repeatedly within a 12-month period.	1. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home 2. Recurrent substance use in situations in which it is physically hazardous 3. Recurrent substance-related legal problems 4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance	1. Substance is often taken in larger amounts or over a longer period than was intended 2. Persistent desire or unsuccessful efforts to cut down or control substance use 3. Time spent in activities to obtain the substance, use the substance, or recover from its effects 4. Strong desire or urge to substance use 5. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home 6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance 7. Giving up important social, occupational, or recreational activities 8. Recurrent substance use in situations in which it is physically hazardous 9. Continuous substance use despite knowledge of having a persistent or recurrent physical or psychological problem 10. Tolerance (need for markedly increased amounts of the substance to achieve intoxication or desired effect OR markedly diminished effect with continued use of the same amount of the substance) 11. Withdrawal (characteristic withdrawal syndrome for the substance OR the same substance is taken to relieve or avoid withdrawal symptoms)
Substance Dependence (≥3 of the following for one month or repeatedly within 12-month period):	Substance Dependence (≥3 of the following within 12-month period):	
1. A strong desire or sense of compulsion to take the substance. 2. Impaired capacity to control substance-taking behavior. 3. A physiological withdrawal state when substance use is reduced or ceased (withdrawal syndrome for the substance OR use of the same substance with the intention of relieving or avoiding withdrawal symptoms). 4. Tolerance to the effects of the substance (need for markedly increased amounts of the substance to achieve intoxication or desired effect OR markedly diminished effect with continued use of the same amount of the substance) 5. Preoccupation with substance use 6. Persisting with substance use despite clear evidence of harmful consequences	1. Tolerance (need for markedly increased amounts of the substance to achieve intoxication or desired effect OR markedly diminished effect with continued use of the same amount of the substance) 2. Withdrawal (characteristic withdrawal syndrome for the substance OR the same substance is taken to relieve or avoid withdrawal symptoms) 3. Substance is often taken in larger amounts or over a longer period than was intended 4. Persistent desire or unsuccessful efforts to cut down or control substance use 5. Time spent in activities to obtain the substance, use the substance, or recover from its effects 6. Giving up important social, occupational, or recreational activities 7. Continuous substance use despite knowledge of having a persistent or recurrent physical or psychological problem	
	Both Substance Abuse and Substance Dependence lead to clinically significant impairment or distress	Substance Use Disorder leads to clinically significant impairment or distress

ICD-10-DCR – International Classification of Disease, 10th revision, Diagnostic Criteria for Research; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th edition

2.2 CATEGORICAL AND DIMENSIONAL ASSESSMENT OF MENTAL DISORDERS

Ever since psychiatry began to form a self-contained area in medical science, the structure and definition of mental disorders have been debated. Back from the time of the first edition of ICD in 1948, diagnostic symptoms relied on categorical definitions of mental disorders. However, with the expanding of theoretical and practical knowledge, this categorical approach has been criticized for insufficiently covering the vast heterogeneity in biological, clinical, and functional profiles of mental disorders both within and across diagnostic boundaries (Clark et al., 1995). Moreover, diagnostic categories, based on qualitative signs and symptoms, do not integrate fundamental neuroscience and genetic findings (Insel et al., 2010).

Discussion on the reliability of current classifications has resulted in including dimensional features in DSM-IV (1994), and their expansion in DSM-5 (2013), while ICD remains a categorically based system. The goal of the dimensional approach is to reflect variations in severity, symptomatology, impairment, and prognosis of categorically defined disorders. It is noteworthy that most DSM criteria still follow a categorical model, including dimensional diagnoses only in section 3 (Kraemer, 2015).

Categorical and dimensional approaches generally complement each other, although sometimes, depending on the context, one system seems to be more beneficial than the other (Kraemer, 2015). For instance, in clinical practice categorical diagnosis is required for making a decision on medical or other treatment, while evaluation of treatment response relies on dimensional assessment. In turn, dimensional diagnoses are preferable for research purposes, as they are more precise in estimation of disorder parameters and hypothesis testing due to sensitive measures of individual differences.

As ICD-10 and DSM-IV largely failed to fulfil the demand to emphasize the behavioural and neurobiological features of mental disorders, the National Institute of Mental Health (USA) initiated the Research Domain Criteria (RDoC) project in 2009. This is a research classification system that conceptualizes mental illnesses as brain disorders and largely includes data from genetics and clinical neuroscience (Insel et al., 2010; Cuthbert & Insel, 2013), fields believed to influence future psychiatric classifications. Indeed, recent large genetic studies indicate a shared genetic basis for schizophrenia, bipolar disorder, and depression (Smoller et al., 2013; Wray et al., 2013). Such findings support the dimensional view of psychiatric diagnostics and represent a modern trans-diagnostic approach to psychiatric research. Indeed,

expanding data demonstrate clinical implications of dimensional or hybrid dimensional-categorical approaches such as more precise conceptualization of core symptoms of psychopathology (e.g. negative symptoms of schizophrenia), assessment of comorbidity of mental disorders, and evaluation of treatment (e.g. intervention for alcohol dependence) (Bjelland et al., 2009; Fazzino et al., 2014; Ahmed et al., 2015).

Overall, agreement exists among experts that simultaneous use of categorical and dimensional systems results in a wider evidence base, enhancing the validity of psychiatric diagnoses and improving medical decision-making.

2.3 EPIDEMIOLOGY COURSE, AND BURDEN OF MENTAL DISORDERS

2.3.1 SCHIZOPHRENIA

Epidemiology

The lifetime prevalence of schizophrenia was long estimated at 1% worldwide, regardless of core sociodemographic parameters. However, such a unified view was questioned in the last decades, as many recent studies have demonstrated not only notable variance in incidence and prevalence rates, but also heterogeneity in risk factors and clinical profiles. Thus, lifetime prevalence of schizophrenia is currently estimated in the general population at 0.4-1.2% (in Finland 0.87%) (Goldner et al., 2002; Saha et al., 2005; Perälä et al., 2007), with a higher incidence in men than in women (McGrath, 2005; McGrath et al., 2008). In 2015, altogether 11 313 patients in specialized psychiatric care in Finland had a diagnosis of schizophrenia (THL, 2017). Furthermore, male gender is associated with earlier age of onset, poorer socio-economic premorbid adjustment, and more severe negative symptoms at onset (Abel et al., 2010; Segerra et al., 2012). In addition to essential genetic (Tienari et al., 2004) and neurodevelopmental mechanisms of schizophrenia (Fatemi & Folsom, 2009), extensive literature demonstrates a significant pathophysiological role of various epigenetic (e.g. low birth weight and infections during pregnancy or childhood) (Rantakallio et al., 1997; Wahlbeck et al., 2001) and environmental factors (e.g. socio-economic problems, childhood adversity, cannabis use, and immigrant or urban background) (Janssen et al., 2004; Large et al., 2011; Owen et al., 2016). Schizophrenia is highly heritable, with rates of up to 80% (Sullivan et al., 2003).

Course

The most common age of onset of schizophrenia in men is 20-28 years and in women 24-32 years (Paus et al., 2008; Eranti et al., 2013), with a predominance in young adults. Onset after the age of 40 years is rare and associated with female gender and a milder course of illness. Often the clinical phase of schizophrenia is preceded by prodromal symptoms such as sleep disturbance, dysphoric mood and anxiety, delusional or grandiose ideas, and functional impairment (Addington et al., 2015). As such symptoms are non-specific, they often go unrecognized, resulting in delayed treatment of psychosis (Fisher et al., 2013). Male gender along with family history of schizophrenia, insidious onset of illness, more negative symptoms, and delayed or irregular treatment are considered factors indicating poor outcome (Jablensky, 2009).

Outcome and burden

Major prospective studies demonstrate that up to half of the patients with schizophrenia have a relatively good outcome, reflected in (full) recovery with no intellectual or social impairment or complete remission (van Os & Kapur, 2009). However, the other half have long-term mental and social problems and require constant support (Owen et al., 2016), which, along with recurrent positive and progressive negative symptoms and medication side-effects, result in low quality of life (Narvaez et al., 2008; Yamauchi et al., 2008). Recent Finnish meta-analyses demonstrated an even lower recovery rates, 13.5% (Jääskeläinen et al., 2013). Furthermore, life expectancy in patients with schizophrenia is reduced by 10-20 years comparing with the general population (Chesney et al., 2014). The major contributors to premature mortality are adverse lifestyle and health behaviour (e.g. smoking, poor diet, and lack of exercise), physical morbidity (e.g. cardiovascular diseases, diabetes mellitus, and pulmonary diseases), and insufficient treatment of physical disorders as well as high suicide rates (Saha et al., 2007; Chesney et al., 2014; Laursen et al., 2014).

In contrast to the clinical perspective, the functional outcome is uniformly much graver. Schizophrenia, along with mood and anxiety disorders, is among the most disabling non-communicable conditions; its contribution to the global burden of diseases is comparable to that of cardiovascular diseases and cancers (Whiteford et al., 2015; Vos et al., 2016). The socio-economic burden arises from both direct expenditures in health and social care and the substantially low employment rate of 10-20% (Marwaha & Johnson, 2004; Murray et al., 2012).

2.3.2 SCHIZOAFFECTIVE DISORDER

Epidemiology

The estimated lifetime prevalence of schizoaffective disorder (SAD) in the general population is 0.32% (Perälä et al., 2007), with 3607 patients in specialized psychiatric care in Finland diagnosed with SAD (NIHW, 2017).

Course

The mean age at onset of SAD (23 years) is comparable to that in schizophrenia (22 years), but slightly lower than that in bipolar disorder (26 years) (Pagel et al., 2013). SAD is more common in women than in men. SAD resembles the profile of bipolar disorder regarding core socio-demographic (educational level, marital status) and clinical (substance abuse episodes, presence of affective symptoms, use of medications) characteristics (Nardi et al., 2005). SAD has a more complicated clinical course, reflected in frequent hospitalizations and suicidality, but shows a better social premorbid adjustment than schizophrenia (Pinna et al., 2014). Moreover, relative to schizophrenia and bipolar disorder, SAD includes more severe delusional and thought disorder symptoms (Mancuso et al., 2105).

Outcome

The outcome profile of SAD is considered more favourable than that of schizophrenia (Harrow et al., 2000). Up to 60% of patients with SAD demonstrate clinical remission, but functional remission has lower estimates of about 25% (Pinna et al., 2014). Poorer outcome is usually predicted by low premorbid functioning, early age at onset, absence of precipitating events or stressors, and predominance of psychotic symptoms (Harrow et al., 2000; Malhi et al., 2008).

2.3.3 BIPOLAR DISORDER

Epidemiology

The lifetime prevalence of bipolar disorder (BD) in the general population varies from 1% to 2.8% (Kessler et al., 2011; Merikangas et al., 2011; Clemente et al., 2015). In 2015, altogether 10 751 patients in specialized psychiatric care in Finland were treated for BD (NIHW, 2017). With growing evidence of the clinical significance of subthreshold BD (Hoertel et al., 2013), concerns that the prevalence of BD is underestimated have emerged. Thus, there is a

tendency towards increasing estimates for prevalence of bipolar disorder spectrum (BD-I, BD-II, or subthreshold BD) (Merikangas & Lamers, 2012; Dell'Aglio et al., 2013). Numerous studies have shown heritability rates of BD to be as high as 60-80% (Taylor et al., 2002).

Course

Although bipolar disorder affects both genders equally, Nivoli et al. (2011) demonstrated some dominance of BD-II in females. The same study revealed more gender-specific characteristics of BD such as predominance of depressive polarity and suicide attempts in women and significant substance use disorders in men. BD onset is usually at a young age, but proper diagnostics may be delayed for years (Suominen et al., 2007).

Bipolar disorder is a lifelong episodic illness with periods of remission. However, recurrence is common, especially in patients with poor treatment adherence. The polarity of the BD episode could be predictable for the subsequent course of illness. Thus, predominance of depressive polarity in more typical for BD-II and often associated with suicidal attempts. In turn, manic pattern relates to younger age at onset and substance misuse (Grande et al., 2016). Moreover, studies have demonstrated that even euthymia in not rare; nearly half of the patients are symptomatic, with a predominance of depressive symptoms during follow-up (Judd et al., 2002 and 2003; Pallaskorpi et al., 2015).

Outcome and burden

The progression of BD is associated with cognitive and functional impairment. Neurocognitive decline is common in all mood states and periods of remission (Martínez-Arán et al., 2004). It is related to severe course of BD, with recurrent manic and psychotic episodes and prolonged duration of illness (Bourne et al., 2013). Along with persisting or residual symptoms (in particular syndromal and subsyndromal depression), cognitive deterioration contributes to the functional impairment of patients with BD, leading to a significant delay of objectively measured functional recovery (reduced scores on impairment scales) compared with syndromal remission (van der Voort et al., 2015), and overall cumulation of work and global functioning problems over time (Goldberg & Harrow, 2011).

In addition to cognitive and functional difficulties, physical morbidity is very common among patients with BD, with predomination of cardiovascular disorders, diabetes, and obesity (Kilbourne et al., 2004). Medical comorbidity indicates worse prognosis and increases mortality among patients with BD. Another strong contributor to premature mortality in BD is death by suicide

(Pallaskorpi et al., 2017), occurring in 6-11% of patients with affective disorders (including BD) (Inskipet al., 1998; Bostwick & Pankratz, 2000; Angst et al., 2005). Although suicide attempts are more common in women, the completing suicide is more common in men than in women (men 8%, women 5%) (Nordentoft et al., 2011).

Because BD affects mainly young adults, i.e. the vocationally and economically active population, the severity and chronicity of illness, with negative impacts on functioning and high mortality rates, substantially contribute to the global burden of disease (Whiteford et al., 2015; Vos et a., 2016) and days out of role (Alonso et al., 2011).

2.3.4 DEPRESSIVE DISORDER

Epidemiology

Depression is a highly prevalent and disabling condition, resulting from the effects of various genetic, biological, psychological, and social risk factors (Kupfer et al., 2012). Estimated lifetime prevalence of depressive disorder in the general population is 20% (Kessler et al., 2003; Kessler et al., 2012), with a tendency of increasing in later years (Markkula et al., 2015). Moreover, many authors have suggested that lifetime prevalence could be underestimated due to methodological limitations of epidemiological studies (Kruijshaar et al., 2005; Moffitt et al., 2010). According to a statistical report on specialized psychiatric care in Finland, 51 072 patients were treated for depressive disorder in 2015 (NIHW, 2017). Depression affects women almost two times more often than men (Pirkola et al., 2005), with, however, similar distributions of age at onset during the lifespan (Kessler et al., 2007). The estimated heritability rate of depression is about 40% (Lohoff, 2010).

Course

Although having episodic course, depression is considered a chronic disease with a high risk of relapse. Thus, the 12-month relapse rate in untreated patients is estimated at 20-37%, and rates of recurrence are also high. Factors increasing the risk of recurrence are female gender, being single, a history of depressive episodes, and longer duration of the previous episode (Richards, 2011).

The co-occurrence of depression with other mental and somatic diseases is very common. The most typical psychiatric lifetime comorbid disorders for

depression are anxiety disorder (up to 73%), personality disorders (45%), and alcohol use disorder (up to 30%) (Melartin et al., 2002). Comorbidity has a substantial negative impact on treatment response and prognosis of depression, especially with comorbid substance use and personality disorders (Markowitz et al., 2007; Lai et al., 2015). In addition to psychiatric comorbidity, depression is often accompanied by somatic diseases such as cardiac diseases, diabetes, obesity, or chronic pain (Kendler et al., 2009; De Hert et al., 2011). Moreover, comorbidity of depression with chronic physical illnesses has a greater adverse effect on health, incrementally worsening health relative to depression alone, any chronic disease alone, or any combination of chronic diseases without depression (Moussavi et al., 2007).

The clinical picture of depression often includes suicidality. In psychological autopsy studies of unselected suicides, about half of all subjects had suffered from depression. The lifetime risk of suicide death in patients with depression is estimated at 7%, with higher rates in men than in women (Isometsä, 2014). Along with male gender, risk factors for suicidal behaviour are previous suicide attempts, more severe course of depression, and family history of psychiatric disorder (Hawton et al., 2013). In addition, comorbid anxiety and substance use disorders are large contributors to suicidality. Thus, prominent physical morbidity and intense suicidal behaviour, along with hazardous health behaviour and biological dysregulations result in increased mortality rates in patients with depression (Cuijpers & Schoevers, 2004).

Outcome and burden

According to the reports of WHO, unipolar depressive disorders are among the ten most disabling diseases worldwide (Lopez et al., 2006; Vos et al., 2016), and are anticipated to take first place in high-income countries and second place globally by 2030 (Mathers & Loncar, 2006). In WHO surveys, depression was linked to 5% of all days out of role, with a leading position among mental disorders and fourth place among all of the disorders considered (Alonso et al., 2011).

Overall, the complex and severe clinical, functional, and comorbidity profile of depression predicts decrements in role functioning and leads to poor quality of life (Koivumaa-Honkanen et al., 2008; Kessler, 2012).

2.3.5 ANXIETY DISORDERS

Epidemiology

Anxiety disorders, including panic disorder with or without agoraphobia, generalized anxiety disorder, social anxiety disorder, and specific phobias, are the most prevalent psychiatric conditions, with lifetime estimates of 16-28% in the general population, with predominance of social phobia, specific phobia and general anxiety disorder (Kessler et al., 2005b; Wittchen et al., 2011; Kessler et al., 2012). The proportion of patients with anxiety disorders in specialized psychiatric care in Finland in 2015 was less than the corresponding proportion of patients with depression, as 21 862 patients were treated for anxiety disorders (NIHW, 2017). For all anxiety disorders, heritability estimates have ranged from 30% to 50% (Shimada-Sugimoto et al., 2015). Despite the heterogeneity of demographic characteristics of anxiety disorders, most studies are in accord regarding their higher prevalence in women than in men, likely resulting from various genetic, neurobiological, and psychosocial factors (Bandelow & Michaelis, 2015).

Course

The median age at onset of anxiety disorders is 11 years (Kessler et al., 2005a). Thus, usually starting in adolescence or early adulthood, anxiety disorders are conceptualized as a chronic condition, with a peak in middle age and a substantial decrease in the elderly. Specific phobias are typical for childhood, whereas social phobia, agoraphobia, and panic disorders emerge in early adulthood, and generalized anxiety disorder in middle age. Regardless of the high prevalence of anxiety disorders, they often go unrecognized or are only poorly treated (Alonso et al., 2007; Baldwin et al., 2012). Overall, the detection and interpretation of anxiety is challenging, as many patients simultaneously have other mental disorders, which lead to overlapping of symptoms and raise the dilemma of anxiety`s psychopathological primarity or secundarity to affective and psychotic symptoms (Achim et al., 2011; Braga et al., 2013). In addition, underestimating of anxiety could be explained by choice of methodological approach since, for example, structured diagnostic interviews alone seem to define subthreshold anxiety less reliably than in combination with additional instruments (Karsten et al., 2011; Braga et al., 2013). Furthermore, the hierarchical principle of psychiatric diagnostics often results in priority of other mental disorders that require intense treatment but are less frequent such as schizophrenia or bipolar disorder (Cassano et al., 1998).

Outcome and burden

Probably due to both high prevalence and treatment issues, anxiety disorders are among the major contributors to the Global Burden of Disease, measured in disability-adjusted life-years lost (DALY). The burden of anxiety disorders exceeds that of schizophrenia spectrum disorders and bipolar disorder, being comparable to that of substance use disorders (Whiteford et al., 2015; Vos et al., 2016).

The rapidly expanding literature shows that not only categorically defined anxiety disorders but also subthreshold states are common and highly disabling. For instance, subthreshold panic and generalized anxiety disorder are associated with increased comorbidity rates with mood or substance use disorders. Moreover, subthreshold anxiety contributes to greater intensity of utilization of primary health care services and use of benzodiazepines (Bystritsky et al., 2010; Haller et al., 2014).

2.3.6 SUBSTANCE USE DISORDERS

Epidemiology

Substance use is a historically pervasive phenomenon worldwide. Current estimates of lifetime prevalence of Substance Use Disorders (SUD) (including both alcohol and drug substances) in the general population vary from 10% to 29% (Wittchen et al., 2011; Grant et al., 2015 and 2016). However, the upper extremities of the prevalence rates are relatively rare, the mean being 1.3-15.0% (Kessler et al., 2007). Of 7461 patients in specialized psychiatric care treated for SUD in 2015, the majority (n=4238) had a diagnosis of alcohol use disorder (NIHW, 2017). The WHO estimate of global smoking prevalence is 21% (WHO, 2015).

Substance use disorders are more common in men than in women and are associated with younger age (Grant et al., 2009; Grant et al., 2015). The heritability of substance use disorders is 30-60% (Wang et al., 2012).

Course

While mostly focusing on alcohol use, numerous studies have indicated that substance use dependence has a chronic course, and substance abuse is a remitting condition (Sarvet & Hasin, 2016). Despite general chronicity, more

than half of the SUD patients remain in remission over a 3-year period (Dawson et al., 2007).

SUD often co-occurs with mental disorders – nearly half of patients with psychiatric illness suffer from some form of SUD over their lifetime (Weaver et al., 2003; Lai et al., 2015), including a 56% lifetime prevalence of smoking (Glasheen et al., 2014; Smith et al., 2014). Furthermore, Grant et al. (2009) demonstrated that alcohol dependence is likely to be predicted by borderline personality disorder, and alcohol abuse by BD-II and dependent personality disorder. In turn, drug dependence was predicted by panic, schizotypal, and narcissistic personality disorders, and drug abuse by BD-I, borderline, schizotypal, and narcissistic personality disorders. While the strong interrelations of SUD, conduct disorders, and antisocial personality disorder are explained by the phenomenon of externalization (Krueger et al., 2001), the relationships between SUD and mood disorders are still under debate. For instance, according to the "precipitation model", SUD cause depression by neurotoxic effects (Brady & Sinha, 2005; Fergusson et al., 2009), whereas the "self-medication model" considers substance use to be a maladaptive coping mechanism for depressive symptoms (Markou et al., 1998; Bolton et al., 2009). Many authors suggest, however, that these two mechanisms are both relevant and vary across the lifetime (Pacek et al., 2013).

Outcome and burden

SUDs are highly disabling, nearly 9% of all years of life lost to death and disability are linked to alcohol, drug, and nicotine use (WHO, 2004). Individuals with alcohol and drug use disorders are at increased risk for physical morbidity such as liver disease, pancreatitis, cardiac diseases, and cancer (Li, 2008; Varela-Rey et al., 2013), and smoking is associated with chronic obstructive pulmonary disease, cancer, and cardiovascular disease (Agustí et al., 2003; Grief, 2011). As a co-occurring condition, SUD worsens course, outcome, and quality of life of mental disorders (Margolese et al., 2004; Whiteford et al., 2015; Nesvåg et al., 2016). Moreover, SUD itself and as a comorbid state is associated with increased suicidal behaviour (Ferrari et al., 2014; Schaffer et al., 2015; Yuodelis-Flores & Ries, 2015), which, along with physical and psychiatric morbidity, results in premature mortality (Chesney et al., 2014; Hjorthøj et al., 2015).

2.4 COMORBIDITY OF MENTAL DISORDERS

2.4.1 INTERNALIZING AND EXTERNALIZING DISORDERS

The structure and classification of mental disorders were permanently in the focus of researchers, clinicians, and health care organizations for almost a century. While the initial focus was on definition and specification of different psychopathologies, the landscape of the modern approach to classification is largely affected by the rapidly growing data on comorbidity of mental disorders (Clark et al., 1995). Thus, comorbidity, as a highly general phenomenon, forced the researchers to alternative conceptualization of psychiatric nosology, which would impact both clinical and research strategies. The strict categorical approach in diagnostics raised concerns about generalizability and validity of studies of participants with only a certain mental disorder. The concerns arose from the fact that such "pure" cases are relatively rare and less severely impaired, and thus, may be unrepresentative of the entire spectrum of the target disorder (Krueger, 1999).

The studies on comorbidity structure initially targeted DSM-III affective and substance use disorders as highly prevalent and disabling, and, more importantly, systematically co-occurring (Kessler et al., 1994). In several works, Krueger (Krueger et al., 1998; Krueger, 1999) demonstrated this co-occurring as fitting into the two higher order and psychologically coherent dimensions of *internalization* and *externalization*. Internalization refers to expression of distress inwards, which is typical for unipolar mood and anxiety disorders, while externalization describes expression of distress outwards, common in substance use and antisocial behaviour disorders. The cluster of internalizing disorders was divided in some studies into two subgroups of "fear" (agoraphobia, social phobia, specific phobia, panic disorder) and "anxious-misery" (major depressive episode, dysthymia, generalized anxiety disorder). However, eventually a two-factor structure, consisting of internalizing and externalizing domains, was found to be superior to describe the correlations between 10 common disorders (Figure 1). Bipolar disorder is likely to form a subfactor within the internalizing domain (Forbush & Watson, 2013), although findings to support this speculation remain unclear.

Further studies demonstrated not only interrelationships of mental disorders, but also linking of mental disorders with dimensions of personality. In particular, internalization was associated with higher negative emotionality (propensity to negative affect such as anxiety, anger, or alienation) and lower positive emotionality (experiencing positive emotions due to active role in work and social activities); externalization, in turn, was related to lower

constraint (constraint = propensity for cautious and restrained behaviour and endorsement of traditional values) (Krueger et al., 2001). Moreover, antisocial and borderline personality disorders are strongly related to the externalizing domain, while internalizing fear factor had significant interactions with schizotypal, borderline, avoidant, and obsessive-compulsive personal disorders (Harford et al., 2013). Furthermore, the personality trait of neuroticism is a significant risk factor for internalizing pathology (Griffith et al., 2010; Ormel et al., 2013), and is also responsible for high comorbidity rates within and between internalizing and externalizing disorders (Khan et al., 2005; Krueger & Markon, 2006). Neuroticism likely mediates underlying genetic diathesis of internalizing disorders (de Moor et al., 2015). Indeed, numerous studies have found broad similarities in the genetic basis of internalizing (Hettema, 2008; Kedler et al., 2011) and externalizing pathology (Krueger et al., 2005).

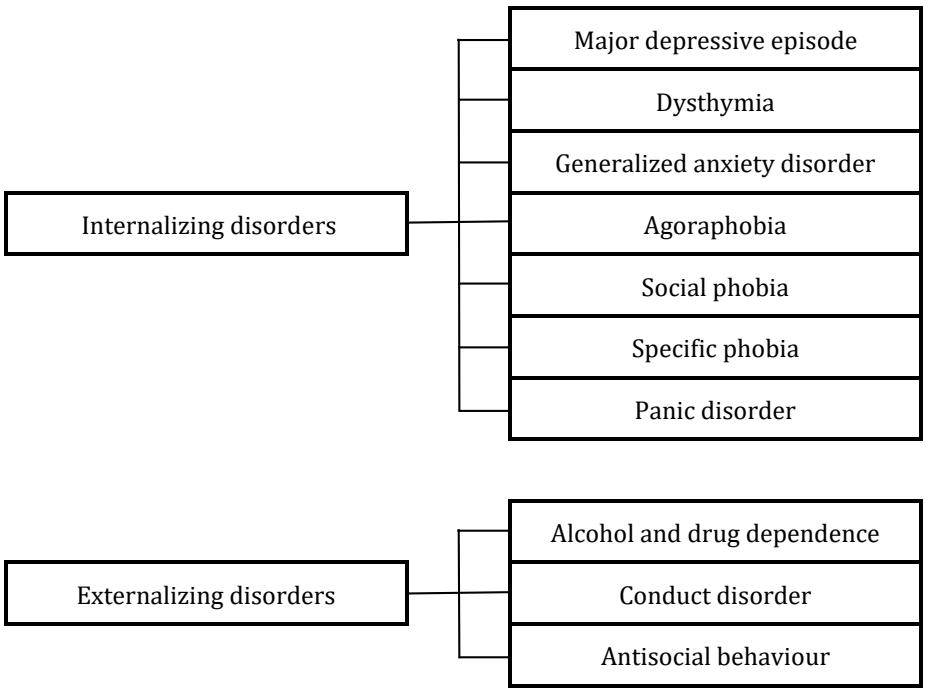

Figure 1. Structure of the two-factor internalizing/externalizing model.

2.4.2 RELATIONSHIPS BETWEEN MENTAL DISORDERS, ANXIETY, AND SUBSTANCE USE

The phenomenon of co-occurring of mental disorders was recognized from the dawn of modern psychiatry and conceptualized as "comorbidity" in the 1970s (Feinstein, 1970). Comorbidity has ever since been in the spotlight of researchers (Kessler et al., 2011; Kushner, 2014). Indeed, large studies have found that nearly half of patients with certain psychiatric illness are likely to have one or more comorbid mental or substance use disorders (Kessler et al., 2005b; Jacobi et al., 2014). The most prevalent psychiatric conditions are also the strongest contributors to comorbidity. For instance, up to 73% of patients with depression, 45% of patients with bipolar disorder, and 38% of patients with schizophrenia have a one or more lifetime anxiety disorders (Brown et al., 2001; Melartin et al., 2002; Achim et al., 2011; Pavlova et al., 2015). Substance use disorders are also highly prevalent comorbid states, emerging in half of the patients with mental disorders (Melartin et al., 2002; Weaver et al., 2003; Lai et al., 2015), with a predominance in patients with schizophrenia (Buckley et al., 2009; Tsai & Rosenheck, 2013). Regarding the group of mood disorders, anxiety and personality disorders are among the most common co-occurring conditions (Melartin et al., 2002; Grant et al., 2005; Mantere et al., 2006), while the role of substance use is also significant, although more prominent in bipolar disorders than in depression.

Comorbid anxiety and substance use disorders are associated with poorer course and outcome of principal psychiatric illness (El-Mallakh & Hollifield, 2008; Braga et al., 2013; Nesvåg et al., 2015) as well as with impaired general quality of life (Saarni et al., 2007; Whiteford et al., 2010; Comer et al., 2011). Furthermore, co-incidence of substance use contributes to increased physical morbidity (Frash et al., 2013) and suicidal behaviour (Schaffer et al., 2015; Yuodelis-Flores & Ries, 2015), both leading to premature mortality (Hjorthøj et al., 2015). Interestingly, not only comorbid anxiety disorders, but also subthreshold anxiety has a negative impact on prognosis and quality of life (Weiller et al., 1998; Karsten et al., 2013; Miloyan et al., 2015), which urges clinicians to careful recognition of affective features at syndromal level.

2.5 ADHERENCE TO TREATMENT

Adherence (also compliance) to treatment is generally conceptualized as accord between a patient´s behaviour and recommendations of a health care professional regarding, for instance, making lifestyle changes or taking a medication (Sabaté, 2003; Hearnshaw & Lindenmeyer, 2006). Thus, non-adherence is a massive obstacle for any kind of treatment to be successful and

is a common problem across medical and psychiatric specialties. Adherence should be viewed from different perspectives, patient-related factors being especially important. Extensive data show that higher age, female gender, and being married and highly educated increase treatment compliance (Senior et al., 2004; Cooper et al., 2005; Fodor et al., 2005). Beyond socio-demographic factors, psychological factors, such as a patient´s expectation about treatment or a negative attitude towards treatment, could substantially decrease adherence (Kilbourne et al., 2005; Leuchter et al., 2014;). As psychiatric treatment is largely based on medication, side-effects, fears of addiction, complexity of medication, and longitudinal course of treatment (also causing structural neurological problems such as brain volume loss) are factors associated with a negative attitude and, in case of brain changes, also memory impairment, leading to discontinuation of treatment (Sansone & Sansone, 2012; Veijola et al., 2014).

Alongside the patient, the physician plays a key role in establishing and maintaining the patient´s attitude. An essential component is the inclusion of qualified information/education of the patients and their relatives (Bäuml et al., 2006; Sansone & Sansone, 2012).

Of disease-related factors, severe course of illness and psychiatric comorbidity (axis I and II disorders, substance use disorders) impact compliance in both medical and psychosocial treatments across major mental disorders (Demyttenaere, 2003; Holma et al., 2010; Gibson et al., 2013; Leclerc et al., 2013; Czobor et al., 2015; Arvilommi et al., 2014).

Poor adherence to treatment in mental disorder patients has a substantial impact on unfavourable treatment outcomes such as lack of remission, increased risk of relapse, and suicidal behaviour (Marder, 2003; Weiden et al., 2004; Colom et al., 2005; Meehan et al., 2006). Furthermore, disrupted and irregular psychiatric treatment contributes to increased health care costs and to the global burden of mental disorders (Svarstad et al., 2001; Gilmer et al., 2004).

2.6 ORGANIZATION OF MENTAL HEALTH CARE SERVICES IN FINLAND

In concordance with the general goals of health care defined by WHO, health care in Finland aims to maintain and improve health and well-being, work, and functional capacity as well as to reduce health inequalities and promote social security. Preventive health care is an essential element of Finnish health care policies, defined by the Ministry of Social Affairs and Health. The fees for health care services provided by health centres are regulated by law. The

majority of healthcare services are provided within the publicly funded system, consisted from primary and secondary (in some fields also tertiary) sectors, although private and occupational healthcare is also available.

Primary health care is organized by municipalities and provided by local health centres. The division into primary and specialized care settings also applies to Finnish mental health services. Currently, primary mental care in the Helsinki metropolitan area is developed within the frames of collaborative care (APA, 2016). This model is characterized by close collaboration of primary (represented by general practitioner and "case manager" (usually nurse)) and specialized (consulting psychiatrist) care. The collaborative care model appears to be more effective than standard care, at least for the treatment of depression and anxiety disorders (Bower et al., 2006; Gilbody et al., 2006). Moreover, if considered eligible by a physician (general physician, private physician, occupational health care physician), primary care patients in the Helsinki metropolitan area could receive short-term internet-based psychotherapy, provided by the Psychiatric Department of the Hospital District of Helsinki and Uusimaa. In 2016, altogether 1895 patients received internet-based psychotherapy.

In serious and complex mental disorders for which primary mental care services are considered insufficient or inappropriate, the primary care/private/occupational health physician can refer the patient to specialized psychiatric care, which provides examinations and treatments within hospital and outpatient settings. According to the Finnish legislation, access to secondary care must be arranged within a certain time period. Psychiatric hospitals in Finland are public and owned by municipalities or joint municipal authorities. Finland is divided into 20 hospital districts that provide specialized medical care. Each hospital district has a central hospital and regional and local (e.g. city) hospitals. In addition, there are five university hospitals located in the cities of Helsinki, Turku, Tampere, Kuopio, and Oulu. University hospitals and central hospitals of the hospital districts are responsible for the most demanding examinations and medical procedures. All of the hospital districts belong to a catchment area of the university hospitals. The majority of evaluations and treatments of mental health disorders take place at the psychiatry outpatient clinics. The clinics have a multidisciplinary team, including psychiatrists, nurses, psychologists, social workers, and, in many clinics, occupational therapists. Visits to the clinics are normally by appointment and are free of charge to the patient. Specialized psychiatric care aims to use research- and evidence-based treatment methods. The treatment and rehabilitation could include psychotherapy or other forms of therapy approved by The Social Insurance Institution of Finland (KELA)

based on the patient's application and accompanied by a medical certificate from a psychiatrist or another attending physician.

Tertiary psychiatric care is provided by university hospitals and focuses on examination and treatment within areas of expertise such as geriatric psychiatry, substance use psychiatry, and neuropsychiatry.

2.7 OBJECTIVE AND SUBJECTIVE ASSESSMENT OF FUNCTIONING

Deficiencies in social, residential, and occupational performances are common in patients with mental disorders. Although functional recovery is crucial in reducing the burden of mental disorders and enhancing the quality of life of the patients, the evaluation of functioning is often challenging or even lacking in clinical practice (Ishak et al., 2013). Functioning could be assessed by using different sources of information such as rating scales completed by the patients or their relatives (Leifker et al., 2011), performance-based measures (Harvey et al., 2007; Depp et al., 2009), and direct observations by clinicians (Kleinman et al., 2009). Moreover, many studies have demonstrated that neurocognition should also be evaluated in functional assessment as a notable predictor of disability (Bowie et al., 2010). The patient´s self-reports or interviews of informants (relatives, friends, or others) often become the instruments of choice, especially in busy clinical practice. However, self-reports are often less reliable than objective evidence derived from a clinician´s observations or performed tests (Durand et al., 2015; Gould et al., 2015; Harvey et al., 2015). Perception and self-rating level of functioning vary between diagnostic groups. For instance, patients with schizophrenia spectrum disorders could overestimate their functioning and work ability (Huppert et al., 2001; Oorschot et al., 2012), partly due to cognitive impairment (Bowie et al., 2007). By contrast, a common phenomenon for patients with mood disorders is an underestimation of functional capacity (Fagiolini et al., 2005; Zimmerman et al., 2012; Pranjic & Males-Bilic, 2014).

2.8 SUMMARY OF THE LITERATURE REVIEW

Major mental disorders are common and disabling, with a clear tendency for co-occurring. The phenomenon of comorbidity of mental disorders is well recognized. However, the impact of co-occurring psychiatric symptoms (e.g. depressive symptoms and anxiety) on the course and functional outcome of principal mental disorders remains unclear. Furthermore, it is poorly known whether the comorbidity profile varies between heterogeneous

psychopathologies. Thus, there is a need to expand the dimensional and trans-diagnostic approach in order to enhance the understanding of the clinical structure of mental disorders.

3 AIMS OF THE STUDY

This study aimed to investigate the prevalence and characteristics of anxiety symptoms and substance use among specialized care patients with schizophrenia or schizoaffective disorders, bipolar disorder, or depressive disorder. Also investigated was whether affective symptoms and substance use could impact adherence to psychiatric treatment, thus influencing level of functioning and ability to work.

Specific aims of Studies I-IV were as follows:

I. To compare point prevalence of comorbid anxiety symptoms and their interrelation with personality traits and symptoms of depression and personality disorders. Anxiety was expected to be less severe in patients with schizophrenia or schizoaffective disorder than in their mood-disordered counterparts.

II. To investigate the prevalence, co-occurrence, and correlates of substance use and smoking, expecting the most severe alcohol use in patients with bipolar disorder and smoking and non-alcohol substance use in patients with schizophrenia spectrum disorders.

III. To evaluate the prevalence and associations for poor adherence to outpatient care and psychopharmacotherapy within in- and outpatients, assuming substance use as a strong contributor to non-adherence.

IV. To investigate the perceived level of functioning and ability to work and objective work status in specialized psychiatric care patients, expecting the highest disability and lowest concordance between subjective and objective measures of work ability in the group of patients with schizophrenia or schizoaffective disorders.

4 MATERIALS AND METHODS

4.1 HELSINKI UNIVERSITY PSYCHIATRIC CONSORTIUM (HUPC)

The HUPC is a pilot research project, performed in collaboration between the Faculty of Medicine of the University of Helsinki, the Department of Mental Health and Substance Abuse Services of the National Institute for Health and Welfare, the Department of Social Services and Health Care of the City of Helsinki, and the Department of Psychiatry of Helsinki University Central Hospital. The catchment area with 1 139 222 inhabitants in 2012 covered the metropolitan area of Helsinki, including the municipalities of Helsinki, Espoo, Vantaa, Kauniainen, Kerava, and Kirkkonummi. The HUPC study was approved by the Ethics Committee of Helsinki University Hospital and the pertinent institutional authorities on 28 August 2010.

4.1.1 SETTING

The HUPC cross-sectional study was carried out between 12 January 2011 and 20 December 2012 in 10 community mental health centres, 24 psychiatric inpatient units, one day-care hospital, and two supported housing units. The online survey was performed between 12 January 2011 and 20 December 2012 using specific notebooks via mobile access, also with the possibility of a paper-and-pencil version. The coordinator of the HUPC project assisted participants with the replying technique. Patients were not rewarded for their participation. The online survey included a large set of psychometrical self-report questionnaires for evaluation of socio-demographic and clinical characteristics of the patients (see below).

4.1.2 SAMPLING

According to the resident population, half of the subjects were sampled from the Department of Psychiatry of Helsinki University Central Hospital and half from the Department of Social Services and Health Care, Psychiatric Services of the City of Helsinki. The stratified sampling was performed by randomly drawing all eligible patients on a certain day or week in a unit or by randomly selecting from patient lists. Within the hospital setting, every fifth voluntary entry was identified. Inpatients receiving involuntary treatment were considered unable to give informed consent according to the Declaration of

Helsinki. Patients aged over 18 years and providing written informed consent were included in the study. The exclusion criteria were mental retardation, neurodegenerative disorders, and insufficient Finnish language skills. Of the 1361 eligible patients, 610 declined to participate and 304 were lost for other reasons. The final number of participants was 447, yielding a response rate of 33%. Register-based analysis of representativeness demonstrated no difference from the patients of participating organizations by gender or age, neither other demographic characteristics of patients in current study differed from representative screening-based Vantaa Depression Study or the Jorvi Bipolar Study in the same catchment area (Melartin et al., 2002; Mantere et al., 2004).

4.2 DIAGNOSTIC ASSESSMENT

Using all available medical records and consulting senior research psychiatrists in any obscure cases, the researchers re-examined clinical diagnoses originally given by attending psychiatrists. Diagnostic assessments were conducted according to the ICD-10-DCR, providing the best-estimated lifetime main diagnosis. Substance use disorders were classified as secondary (comorbid) diagnoses with differentiation to alcohol use disorders and other substance use-related diagnoses.

4.2.1 PATIENTS

Patients were divided into three subgroups according to the most common principal diagnoses: schizophrenia (F20.00-F20.9) or schizoaffective disorder (F25.00-F25.9) (SSA, n=113), bipolar disorder (F31.00-F31.9) (BD, n=99), and depressive disorder (F32.00-F33.9, F34.1) (DD, n=188). In Studies I, III, and IV, patients with a principal diagnosis of anxiety disorder, eating disorder, neuropsychiatric disorder, or substance use disorder (n=47) were excluded from the final analyses due to the low number of patients in each group, producing a total number of patients of 400. Only Study II included all 447 participants, retaining three main diagnostic groups. See **Table 6** for the main socio-demographic and clinical characteristics of the sample.

Table 6. Sociodemographic and clinical characteristics of the sample

	SSA		BD		DD		Total		p-value
	n	%	n	%	n	%	n	%	
Number	113	28.3	99	24.8	188	46.9	400	100.0	
Female	54	47.8	63	63.6	146	77.7	263	65.8	<0.001[1]
Marital status									<0.001[1]
Married/cohabitating	10	9.1	37	37.4	68	36.6	115	29.1	
Divorced/widowed	19	17.3	30	30.3	39	21.0	88	22.3	
Unmarried	81	73.6	32	32.3	79	42.4	192	48.6	
Cohabitation status									<0.001[1]
Single	63	57.3	36	36.4	77	41.4	176	44.6	
Cohabitating	22	20.0	51	51.5	95	49.1	168	42.5	
Residential communities*	25	22.7	12	12.1	14	7.5	51	12.9	
No children	97	89.0	58	59.8	130	70.7	285	73.1	<0.001[1]
Vocational education	68	61.8	71	71.7	121	65.1	260	65.8	0.307[1]
Smokers**	57	51.8	50	50.5	78	42.2	185	47.0	0.197[1]
SUD diagnosis	35	31.0	38	38.4	36	19.1	109	27.3	0.004[1]
AUD diagnosis	25	22.1	30	30.3	29	15.4	84	21.0	0.012[1]
Inpatients	36	31.9	20	20.2	34	18.1	90	22.5	0.028[1]
Age, mean (SD)	44.3 (12.4)		43.4 (12.3)		41.2 (13.3)		42.0 (13.0)		0.002[2]
Number of hospitalizations, mean (SD)	2.0 (1.1)		1.5 (1.3)		0.9 (1.2)		1.4 (1.3)		<0.001[2]

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

SUD = substance use disorder (including AUD); AUD = alcohol use disorder

* or any other type of residence, ** smoking daily or occasionally

[1] Chi-square test, [2] Kruskall-Wallis test (between-group comparison)

4.3 MEASUREMENTS AND ASSESSMENTS

4.3.1 SOCIO-DEMOGRAPHIC VARIABLES

Data on all socio-demographic variables were collected from patients´ reports.

4.3.2 SELF-REPORT SCALES

4.3.2.1 Overall Anxiety Severity and Impairment Scale (OASIS)

The OASIS (Norman et al., 2006 and 2011) is a five-item self-report questionnaire developed as a continuous measure of severity and impairment associated with anxiety disorder(s) or subthreshold anxiety during the past week. Several recent studies in non-clinical and clinical samples (including psychiatric secondary care) have demonstrated high internal consistency and strong reliability and validity of the OASIS (Cumbell-Sills et al., 2009; Ito et al., 2015; Bragdon et al., 2016). In the current study, we used the Finnish version of the OASIS, created by Professor Erkki Isometsä. The translation was revised in collaboration with the developer of OASIS, Dr. Sonya Norman. The OASIS includes five questions on the frequency and severity of anxiety symptoms, anxiety-related avoidance behaviour, and impaired functioning at home/work/school and in social life. The response scale ranges from zero (no anxiety and no anxiety-related issues) to four (extreme anxiety and massive anxiety-related issues), with a maximum score of 20. A recommended cut-off score for screening of anxiety disorder is eight points (Campbell-Sills et al., 2009). Cronbach's alpha for OASIS was 0.84, showing good internal consistency.

4.3.2.2 Beck Depression Inventory (BDI)

The BDI (Beck et al., 1961) is a 21-item self-report questionnaire for measuring severity of depressive symptoms within a one-month period in different settings, including a psychiatric sample (Wang & Gorenstein, 2013). The items comprise mood symptoms such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, and physical symptoms such as fatigue, weight loss, and lack of interest in sex. Each item is rated from zero (no symptoms) to three (severe symptoms). The standard cut-offs are 9 and below for minimal depression, 10 – 18 for mild depression, 19 – 29 for

moderate depression, and 30 – 63 for severe depression. Cronbach's alpha for BDI was 0.91, showing good internal consistency.

4.3.2.3 Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT (Babor et al., 1992) is a 10-item self-report questionnaire assessing alcohol consumption (Hazardous Alcohol Use domain), alcohol-related problems (Harmful Alcohol Use domain), and alcohol dependence symptoms (Dependence Symptoms domain) within the past year. Six items on the frequency of alcohol use behaviour are scored on a scale from zero (never) to four (daily or almost daily). Other items are also scored on a 0 – 4 point scale, although they vary in quantity of response options. An AUDIT score of ≥8 for men and ≥7 for women indicates harmful alcohol use. The AUDIT is a reliable and valid instrument for use among patients with mental illness (Maisto et al., 2000; Dawe et al., 2000). Cronbach's alpha for AUDIT was 0.90, showing good internal consistency.

4.3.2.4 Psychiatric Research Interview for Substance and Mental Disorders (PRISM)

The screen questionnaire of PRISM (Hasin et al., 1996) includes two 10-item scales. The time-frame for both scales is 12 months. The first scale requires whether patient used non-alcohol substance at least six times, the second scale requires whether patient used non-alcohol substance at least for three consecutive days.

4.3.2.5 Sheehan Disability Scale (SDS)

The SDS (Sheehan, 1983; Sheehan et al., 1996) is a three-item self-report questionnaire to assess functional impairment at work, in social life, or in leisure activities, and home life or family responsibilities during a one-week period. Items are scored from zero to 10. Responses can be scored into a single dimensional scale of global functional impairment ranging from zero (no impairment) to 30 (high impairment). Such scoring was used in this study. Although SDS has no recommended cut-off score, five and more points on any scale suggests significant functional impairment. The SDS is demonstrated as a valid measurement in psychiatric patients (Leon et al., 1992; Arbuckle et al., 2009). Cronbach's alpha for total SDS was 0.80, showing good internal consistency.

4.3.2.6 "Short Five" (S5)

The S5 (Konstabel et al., 2012) is a 60-item questionnaire for measuring 30 features of the Five-Factor Model identified by the NEO (Neuroticism-Extraversion-Openness) Personality Inventory (Costa & McCrae, 1992). The S5, thus, assesses the personality traits of Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness using six dichotomous items for each trait. Cronbach's alpha for S5 N was 0.84, for S5 E 0.80, for S5 O 0.69, for S5 A 0.58, and for S5 C 0.75.

4.3.2.7 McLean Screening Instrument (MSI) for Borderline Personality Disorder

The MSI (Zanarini et al., 2003) is a 10-item self-report screening instrument for lifetime borderline personality disorder (BPD). The items are based on DSM-IV diagnostic criteria for BPD and dichotomously rated from zero (no symptom) to one (presence of symptom) with a maximum composite score of 10. A score of seven or higher has been commonly determined as a reliable diagnostic cut-off. The validity of the MSI in a psychiatric care sample was previously demonstrated (Melartin et al., 2009), and MSI has been successfully used in recent clinical studies (Baryshnikov et al., 2015). Cronbach's alpha for MSI was 0.92, showing good internal consistency.

4.3.2.8 General Self-Efficacy scale (GSE)

The GSE (Schwarzer & Jerusalem, 1995) is a 10-item self-report instrument to assess perceived self-efficacy of coping and adaptation abilities in stressful life events. Individuals rate each item using a 4-point scale from one (not at all true) to four (exactly true) with a maximum composite score of 40. Higher score indicates better self-efficacy. The scale is a reliable and valid measure of the perception of self-efficacy in a psychiatric care sample (De Las Cuevas & Penate, 2015). Cronbach's alpha for GSE was 0.93, showing good internal consistency.

4.3.2.9 Trauma and Distress Scale (TADS)

The TADS (Patterson et al., 2002) is a 43-item self-report scale developed for the assessment of traumatic experiences and distress in the form of emotional, physical, and sexual abuse, and emotional and physical neglect during

childhood and early adulthood. Each item is rated from zero (never) to four (almost always). The validity of the TADS was demonstrated in the recent study of Salokangas et al. (2016). Cronbach's alpha for TADS was 0.63, indicating acceptable internal consistency.

4.3.2.10 Experiences in Close Relationships, revised questionnaire (ECR-R)

The ECR-R (Fraley et al., 2000) is a 36-item self-report measure of adult attachment style in two dimensions: Attachment Anxiety (items 1 – 18) and Attachment Avoidance (items 19 – 36). Individuals rate each of the 36 items using a 7-point scale from one (strongly disagree) to 7 (strongly agree), with a higher score indicating greater anxiety and/or avoidance. The ECR-R demonstrated good validity in a psychiatric care sample (Kooiman et al., 2013). Cronbach's alpha for the ECR anxiety scale was 0.95 and for the avoidance scale 0.97, indicating excellent internal consistency.

4.3.3 SMOKING

Using the original questionnaire of Holma et al. (2013), patient responded to statements about their smoking behaviour and smoking history ("never smoked", "quit smoking", "smoke occasionally", and "smoke daily") and the number of cigarettes smoked per day.

4.3.4 SELF-REPORTED TREATMENT ADHERENCE

Patients assessed their adherence to outpatient visits and to psychopharmacotherapy with the question "How often during the current treatment have you attended outpatient visits/used the prescribed psychiatric medication?" In Study III, response options were scaled from zero (never) to three (regularly). The attitude towards outpatient visits and medication was ranked on a scale from zero (negative) to three (highly positive). Patients also classified their satisfaction with current psychiatric outpatient treatment (from unsatisfied to highly satisfied) and their motivation for treatment (low-moderate-high).

4.3.5 WORK STATUS AND ABILITY TO WORK

The researchers verified the patient's current work/employment status by collecting data from medical records and certificates (for sick leave or disability pension). The generated three-item nominal variable of work status (working, sick leave, or disability pension/rehabilitation subsidy) was modified for further analyses in Study IV into the dichotomous variable of working or not working (being on sick leave or disability pension/rehabilitation subsidy). Patients classified their perceived ability to work as "able to work", "reduced work ability", and "unable to work". This was transformed into the dichotomous variable of able to work (able to work and reduced work ability) or unable to work. Data on work status were considered to be objective and data on perceived ability to work to be subjective.

4.4 STATISTICAL ANALYSES

All self-reported symptoms and trait scales were used as continuous variables. In all of the studies, relationships between nominal or ordinal variables were explored with Chi-square test; in case of small sample size, Fisher's exact test was applied. In univariate analyses, T-test was used to estimate the distribution of continuous variables across dichotomous variables and ANOVA across non-dichotomous nominal or ordinal variables. Respectively, Mann-Whitney U-test and Kruskal-Wallis test were used for skewedly distributed variables. The relationships between continuous variables were tested with Spearman`s bivariate correlation analysis. Regression analyses included only variables that were associated most consistently across all diagnostic groups with a dependent variable in univariate or correlation analyses. A probability level of $p<0.05$ was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM, 2013).

4.4.1 STUDY I

The OASIS was a dependent variable in regression analysis to estimate associations with BDI, S5 N, MSI, GSE, and TADS. In addition, not correlated but clinically relevant variables of sex and age were included in the analysis. Separate regression models were constructed for each diagnostic group. As an additional analysis and partly to avoid multicollinearity, regression analysis was performed for all independent variables and then with BDI and S5 N excluded one at a time and simultaneously.

4.4.2 STUDY II

The nominal and ordinal variables of substance use disorders and smoking were analysed *per se* and as dichotomously recoded (patients with or without alcohol use disorder; daily smokers or non-smokers). Patients were designated as "AUDIT-positive" if collected AUDIT scores exceeded the gender-specific cut-off. Relationships between AUDIT, smoking, and clinical measurements were analysed with linear regression model, additionally adjusted for principle diagnoses (SSA, BD, and DD). Interaction analyses were performed to investigate the effect of principle diagnoses on independent variables. Logistic regression analysis was also used to explore the contribution of different variables to smoking status.

4.4.3 STUDY III

Ordinal variables of treatment adherence (outpatient visits and pharmacotherapy) were analysed *per se* and as dichotomously recoded (adherent or non-adherent). The group of "adherent to outpatient visits" included patients who reportedly attended outpatient appointments regularly or partly regularly, as such frequency would enable implementation of the treatment program. The group of "adherent to pharmacotherapy" was formed only by patients who reportedly used their medication regularly. Logistic regression models were built for independent variables of treatment setting (hospital or outpatient unit) and diagnosis of SUD (presence or absence of diagnoses). Sex and age were added as clinically important parameters. The main regression model included all variables, and the additional model excluded treatment setting, as treatment in hospital could be a consequence of poor treatment adherence.

4.4.4 STUDY IV

The SDS was a dependent variable in linear regression models with BDI, OASIS, and GSE. Analogously to previous studies, clinically important variables of age, age at onset, and number of hospitalizations were included in analyses. All logistic regression analyses were performed in the same fashion and investigated associations between objective and subjective ability to work with age, age at onset, number of hospitalizations, BDI, OASIS, GSE, and SDS. In linear models, SDS excluded work domain to avoid cross-loading of two different self-report work ability measures.

4.5 PERSONAL INVOLVEMENT

The author participated in collecting and analyzing the material for the study and took an active role in medical record-based verification of clinical diagnoses. All statistical analyses were performed by the author. The author is the lead author in all four original publications.

5 RESULTS

5.1 STUDY I: ANXIETY SYMPTOMS IN MAJOR MOOD AND SCHIZOPHRENIA SPECTRUM DISORDERS

From 40.2% to 55.6% of patients in all groups reported experiencing anxiety frequently or constantly; from 41.2% to 43.8% assessed their anxiety as severe or extreme (Table 7). SSA patients had lower mean OASIS score (p=0.040), felt frequent or constant anxiety less often (p=0.010), and avoided anxiety-provoking situations less often (p=0.009) than BD and DD patients.

OASIS correlated mainly with the same scales in all groups (Table 8). Of all the correlations, the strongest associations emerged between anxiety and depressive symptoms, and anxiety and high neuroticism. A weak direct correlation of anxiety symptoms with anxious attachment style (ECR anxiety) was observed in all groups (SSA: $r = 0.350$, $p \leq 0.01$; BD: $r = 0.365$, $p \leq 0.001$; DD: $r = 0.273$, $p \leq 0.01$), and with avoidant attachment style (ECR avoidance) in the BD ($r = 0.232$, $p \leq 0.05$) and DD groups ($r = 0.203$, $p \leq 0.05$).

The BDI and S5 N were the most strongly associated with OASIS in regression models (Table 9). When they were excluded from the regression analysis, the MSI and GSE acquired a regression weight in all diagnostic groups and the TADS in the BD and DD groups.

5.2 STUDY II: PSYCHOACTIVE SUBSTANCE USE IN SPECIALIZED PSYCHIATRIC CARE PATIENTS

The mean AUDIT score was higher in men than in women ($p < 0.001$), in younger patients ($r = -0.150$, $p = 0.023$), and in patients with BD rather than SSA or DD ($p = 0.007$) (Table 10). The mean AUDIT score in AUDIT-positive patients clearly exceeded the gender-specific cut-off scores (15.4 ± 6.7 in men and 13.9 ± 7.0 in women). Of these patients, only 40.9% had an AUD diagnosis. Those without diagnoses had, however, a mean AUDIT score of 13.7 for men and 11.6 for women, more than half (7.4 and 6.7, respectively) of which originated from the domains of dependence symptoms and harmful alcohol use.

Table 7. OASIS mean scores and item score distributions between diagnostic groups (Study I).

	SSA (n = 113)		BD (n = 99)		DD (n = 188)	
OASIS score, mean (SD)*	9.4 (5.5)		10.8 (4.4)		11.0 (4.8)	
Distribution of responses to OASIS items by diagnostic groups	n	%	n	%	n	%
How often have you felt anxious?**						
No anxiety	18	16.1	4	4.0	10	5.3
Infrequent or Occasional anxiety	49	43.8	44	44.5	73	39.0
Frequent or constant anxiety	45	40.2	51	51.5	104	55.6
When you have felt anxious, how intense or severe was your anxiety?						
Little or None	16	14.3	3	3.0	7	3.7
Mild or Moderate	47	42.0	50	55.6	103	55.1
Severe or Extreme	49	43.8	41	41.4	77	41.2
How often did you avoid situations, places, objects, or activities because of anxiety or fear?***						
None	23	20.4	14	14.1	20	10.6
Infrequent or Occasional	61	54.0	43	43.4	88	46.8
Frequent or All the time	29	25.7	42	42.4	80	42.6
How much did your anxiety interfere with your ability to do the things you needed to do at work, at school, or at home?						
None	27	24.1	11	11.1	18	9.6
Mild or Moderate	47	42.0	48	48.5	94	50.3
Severe or Extreme	38	33.9	40	40.4	75	40.1
How much has anxiety interfered with your social life and relationships?						
None	22	19.6	8	8.1	16	8.6
Mild or Moderate	50	44.6	58	58.5	90	48.1
Severe or Extreme	40	35.7	33	33.4	81	43.3

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder
*p = 0.040; **p = 0.010; ***p = 0.009 (Kruskal-Wallis test)

Table 8. Spearman's correlation between OASIS and other rating scales by diagnostic group* (Study I).

	BDI	S5 N	MSI	GSE	TADS
SSA (n = 113)	.700	.712	.588	-.448	.498
BD (n = 99)	.729	.569	.447	-.398	.498
DD (n = 188)	.700	.584	.457	-.440	.413

*all correlations at $p \leq 0.001$

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

OASIS = Overall Anxiety Severity and Impairment Scale score; BDI = Beck Depression Inventory score; S5 N = "Short Five" Neuroticism Scale score; MSI = McLean Screening Instrument for Borderline Personality Disorder score; GSE = General Self-Efficacy scale score; TADS = Trauma and Distress Scale score

For findings on smoking status, see Table 11. The mean AUDIT score was higher in daily smokers than in non-smokers ($p<0.001$). The self-reported use of illicit drugs and the proportion of patients with SUD diagnosis other than AUD were fairly low; see Table 12 for details.

In total, 32.6% of patients neither smoked daily nor had SUD diagnoses, AUDIT-measured hazardous or harmful alcohol use, or any 12-month history of using illicit drugs.

In linear regression analysis (Table 13), higher AUDIT score was associated with male gender, daily smoking, symptoms of anxiety, borderline personality, and low conscientiousness. SSA was associated with lower alcohol consumption than BD and DD. Smoking behaviour did not interrelate with any analysed measurement scales in the logistic regression model.

Table 9. Linear regression analysis of clinical correlates for OASIS by diagnosis group (Study I).

All variables included						
	SSA (n = 113)		BD (n = 99)		DD (n = 188)	
	B	Sig.	B	Sig.	B	Sig.
Sex	-.845	.396	-.647	.370	-.595	.415
Age	-.005	.900	.037	.219	.036	.127
BDI	.081	.213	.198	**<.001**	.180	**<.001**
S5 N	.148	**.007**	.086	.053	.094	**.007**
MSI	.388	.084	.008	.966	.214	.152
GSE	-.007	.934	.072	.330	.007	.913
TADS	.011	.674	.029	.094	.021	.110
ECR anxiety	.024	.214	.002	.879	-.014	.271
S5 N excluded						
Sex	-1.008	.338	-.888	.222	-.368	.620
Age	-.014	.741	.022	.450	.038	.117
BDI	.181	**.002**	.218	**<.001**	.204	**<.001**
MSI	.585	**.011**	.169	.331	.382	**.007**
GSE	-.090	.257	-.001	.982	-.061	.320
TADS	.050	.998	.023	.181	.018	.177
ECR anxiety	.031	.129	.012	.450	-.007	.564
BDI excluded						
Sex	-.815	.415	-.749	.368	-.499	.540
Age	.001	.981	.053	.126	.037	.159
S5 N	.184	**<.001**	.145	**.004**	.144	**<.001**
MSI	.410	.069	.124	.565	.257	.122
GSE	-.017	.836	.002	.979	-.106	.123
TADS	.019	.456	.050	**.011**	.043	**.003**
ECR anxiety	.025	.208	.000	.981	-.020	.170
S5 N and BDI excluded						
Sex	-1.042	.356	-1.202	.163	-.104	.903
Age	-.002	.969	.029	.402	.041	.145
MSI	.812	**.001**	.436	**.030**	.544	**.001**
GSE	-.189	**.018**	-.144	**.045**	-.242	**<.001**
TADS	.017	.554	.043	**.035**	.043	**.005**
ECR anxiety	.038	.084	.016	.390	-.010	.511

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

BDI = Beck Depression Inventory score; S5 N = "Short Five" Neuroticism Scale score; MSI = McLean Screening Instrument for Borderline Personality Disorder score; GSE = General Self-Efficacy scale score; TADS = Trauma and Distress Scale score; ECR anxiety = Experiences in Close Relationships questionnaire items 1 – 18

Table 10. Characteristics of AUDIT-measured alcohol use (Study II).

	SSA (n = 113)		BD (n = 99)		DD (n = 188)		Total (n = 447)	
AUDIT scores, mean (SD)								
All*	6.8 (7.3)		8.7 (7.5)		6.7 (7.4)		7.5 (7.8)	
Male**	8.4 (7.7)		11.1 (7.0)		9.1 (8.4)		9.5 (8.3)	
Female	5.0 (6.4)		7.4 (7.5)		5.9 (6.9)		6.6 (7.4)	
AUDIT-positive								
Patients with AUD								
Male	17.3 (7.3)		15.3 (4.6)		17.1 (7.1)		17.7 (7.5)	
Female	16.3 (5.9)		16.1 (7.9)		17.5 (8.4)		18.4 (8.9)	
Patients without AUD								
Male	12.8 (3.6)		14.6 (4.5)		14.4 (8.6)		13.7 (5.5)	
Female	12.7 (4.1)		12.5 (4.8)		11.3 (4.5)		11.6 (4.3)	
AUDIT-positive	n	%	n	%	n	%	n	%
All	44	38.9	53	53.5	71	37.8	193	43.1
Male[a]	29	50.0	25	69.4	20	47.6	82	53.9
Female[b]	15	27.8	28	44.4	51	35.2	111	37.8
Without AUD								
Male	17	58.6	13	52.0	12	60.0	46	56.1
Female	9	60.0	16	57.1	34	66.6	72	64.9

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder
AUDIT = Alcohol Use Disorders Identification Test score; AUDIT-positive = AUDIT score ≥ 8 for men and ≥ 7 for women; AUD = Alcohol Use Disorder
* $p = 0.028$ (Kruskal-Wallis test, between-group comparison)
** $p = 0.011$ (SSA), $p = 0.007$ (BD), $p = 0.008$ (DD), $p < 0.001$ (Total) (Mann-Whitney test, male/female comparison)
[a] of all male patients, [b] of all female patients

Table 11. Smoking status and characteristics of daily smoking (Study II).

	SSA		BD		DD		Total	
	n	%	n	%	n	%	n	%
Smoking status[1]								
Never smoked	28	25.5	27	27.3	63	34.1	136	30.8
Quit smoking	25	22.7	22	22.2	44	23.8	97	22.0
Occasional smoking	8	7.3	11	11.1	14	7.6	39	8.8
Daily smoking	49	44.5	39	39.4	64	34.6	169	38.4
male[a]		50.0		36.1		36.6		40.3
female[b]		38.9		41.3		34.0		37.3
Daily smokers								
Cigarettes per day, mean (SD)[2]	18.9 (8.7)		16.2 (7.2)		15.0 (7.2)		16.4 (7.7)	
AUDIT scores, mean (SD)[3]	8.1 (7.2)		10.8 (7.8)		9.6 (8.5)		9.8 (8.7)	

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

AUDIT = Alcohol Use Disorders Identification Test score

[1] p = 0.443 (Chi-square test), [2] p = 0.334, [3] p = 0.329 (Kruskall-Wallis test (between-group comparison))

[a] of all male patients, [b] of all female patients

Table 12. Use of illicit drugs (Study II).

	SSA (n = 113)		BD (n = 99)		DD (n = 188)		Total (n = 447)	
	n	%	n	%	n	%	n	%
SUD diagnosis	10	8.9	8	8.0	7	3.6	28	6.5
Cannabis	5	4.4	–	–	1	0.5	7	1.7
Sedative or anxiolytic	–	–	4	4.0	2	1.0	7	1.7
Other stimulant	1	0.9	1	1.0	–	–	2	0.4
Inhalant	1	0.9	–	–	–	–	1	0.2
Other psychoactive	3	2.7	3	3.0	4	2.1	11	2.5
Self-reported use at least six times within the last 12 months								
Cannabis	6	5.3	9	9.0	5	2.7	25	5.6
Other than cannabis*	6	5.3	8	8.0	13	6.9	34	7.6

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder
SUD = substance use disorder (other than alcohol use disorder)
* cocaine, heroin, hallucinogens, stimulants, and opioids (misuse of prescription pain medication)

Table 13. Linear regression analysis of clinical correlates for AUDIT adjusted for principal diagnoses as dichotomous variables (Study II)

	Unstandardized coefficient (B)	Sig.
Sex	-.625	<.001
Daily smoking	.750	<.001
Cigarettes per day	.011	.306
OASIS	.047	.011
MSI	.063	.036
S5 N	.001	.868
S5 C	-.018	.008
BDI	.013	.103
TADS	.005	.252
SSA	-.505	.027
BD	-.020	.930
DD	-.255	.243

AUDIT = Alcohol Use Disorders Identification Test score; OASIS = Overall Anxiety Severity and Impairment Scale score; MSI = McLean Screening Instrument for Borderline Personality Disorder score; S5 N = "Short Five" Neuroticism Scale score; S5 C = "Short Five" Conscientiousness Scale score; BDI = Beck Depression Inventory score; TADS = Trauma and Distress Scale score
SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

5.3 STUDY III: SELF-REPORTED TREATMENT ADHERENCE AMONG PSYCHIATRIC IN- AND OUTPATIENTS

The vast majority of patients reported attending outpatient visits (partly) regularly, using prescribed psychiatric medication regularly, and being generally positive about and satisfied with psychiatric treatment (Table 14). Non-adherence to outpatient visits was significantly more common in inpatients than in outpatients ($p<0.001$ in all groups) and in patients with a diagnosis of SUD than in those without this diagnosis ($p = 0.002$ in SSA, $p = 0.005$ in BD, and $p < 0.001$ in DD). Adherence to visits was significantly poorer in inpatients with SUD than in outpatients with SUD ($p<0.001$ in SSA, $p=0.001$ in BD, and $p=0.007$ in DD). Inpatients had a long-term mental care history; the mean overall duration of psychiatric treatment was 21.9 years in SSA, 11.4 years in BD, and 8.8 years in DD groups. Ninety-four percent of non-adherent SSA inpatients utilized psychiatric care for over one year; the respective proportions for BD and DD patients were 85% and 79%. Subjects

with SSA and DD who reported adherence to outpatient visits were less often treated in hospital than their non-adherent counterparts (p=0.021 and p<0.001, respectively). Findings on associations between adherence to outpatient visits and self-report measurements were inconsistent.

In logistic regression analysis, treatment setting was most strongly and consistently associated with adherence to outpatient visits across the diagnostic groups (SSA: B = -2.418, p < 0.001; BD: B = -3.417, p < 0.001; DD: B = -2.766, p < 0.001). The diagnosis of SUD had a regression weight in the main model in SSA (B = -1.686, p = 0.003) and DD (B = -1.380, p = 0.012) patients, and in all diagnostic groups in the additional analyses (SSA: B = -1.555, p = 0.001; BD: B = -1.535, p = 0.006; DD: B = -2.258, p < 0.001). Adherence to psychiatric medication was not associated with any analysed variables in the logistic regression model.

Table 14. Adherence to and attitude towards psychiatric outpatient care* (Study III).

	SSA (n = 113)		BD (n = 99)		DD (n = 188)	
	n	%	n	%	n	%
Attendance to outpatient visits						
Inpatients						
Never or Irregular	20	58.8	15	75.0	21	63.6
Partly irregular or Regular	16	41.2	5	25.0	13	36.4
Outpatients						
Never or Irregular	10	13.1	6	7.6	11	7.2
Partly irregular or Regular	66	86.9	73	92.4	141	92.8
Attitude towards outpatient visits						
Negative or Neutral	28	27.2	21	22.2	33	17.9
Positive or Highly positive	75	72.8	74	77.8	151	82.1
Use of psychiatric pharmacotherapy						
Never or Irregular	18	16.3	28	28.3	36	19.4
Regular	92	83.7	71	71.7	150	80.6
Attitude towards psychiatric pharmacotherapy						
Negative or Neutral	33	30.0	28	28.3	78	41.7
Positive or Highly positive	77	70.0	71	71.7	109	58.3
Satisfaction with treatment						
Dissatisfied or Neutral	34	30.6	25	25.3	52	27.8
Satisfied or Highly satisfied	77	69.4	74	74.7	135	72.2
Motivation for treatment						
Low	7	6.3	1	1.0	2	1.1
Moderate	17	15.3	16	16.2	36	19.3
High	87	78.4	83	83.8	149	79.6

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

* items´ between-group comparison performed with Kruskal-Wallis test, all p > 0.05

5.4 STUDY IV: LEVEL OF FUNCTIONING, PERCEIVED WORK ABILITY, AND WORK STATUS AMONG PSYCHIATRIC PATIENTS WITH MAJOR MENTAL DISORDERS

Of all diagnostic groups, self-reported functional impairment was highest in subjects with DD and lowest in subjects with SSA (Table 15). In linear regression analysis, BDI was the only measure associated with SDS across all diagnostic groups (SSA: B = 0.15, p = 0.026; BD: B = 0.35, p < 0.001; DD: B = 0.30, p < 0.001), while OASIS had a regression weight in SSA (B = 0.40, p = 0.007) and BD (B = 0.44, p = 0.032) groups, and GSE in SSA (B = -0.24, p = 0.006) and DD (B = -0.20, p = 0.010) groups.

Nearly one-third of patients with BD and DD remained at work, while the corresponding proportion of SSA patients was only 5.3% (Table 16).

The proportions of patients working and subjectively able to work correlated moderately strongly and significantly among BD and DD patients (r = 0.58, p<0.001 and r = 0.55, p<0.001), but not in the SSA group (r = 0.09, p=0.379).

Logistic regression analysis of work status demonstrated associations of disability with high SDS scores and high number of hospitalizations (Table 17). Older age and earlier onset had regression weight in the BD group, and low self-efficacy in the SSA group. In the analysis for subjective ability to work, SDS had regression weight in BD and DD groups, and BDI in all groups.

Table 15. Distribution of Sheehan Disability Scale scores by domains across diagnostic groups (Study IV).

Mean (SD)	SSA (n = 113)	BD (n = 99)	DD (n = 188)
SDS summary [1]	16.3 (7.7)	17.7 (7.9)	20.9 (7.6)
work [1]	6.3 (3.2)	6.7 (3.3)	7.3 (3.0)
social life or leisure activities [1]	5.5 (3.1)	5.7 (3.0)	6.9 (2.9)
family life or home responsibilities [2]	4.4 (3.3)	5.3 (2.9)	6.4 (2.9)

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

SDS = Sheehan Disability Scale score

[1] p < 0.001, [2] p = 0.019 (Kruskall-Wallis test)

Table 16. Objective work status and subjective ability to work (Study IV).

	SSA (n = 113)		BD (n = 99)		DD (n = 188)	
	n	%	n	%	n	%
Objective work status [1]						
Working	6	5.3	29	29.3	62	33.0
Sick leave	6	5.3	12	12.1	41	21.8
Disability pension/ Rehabilitation subsidy	101	89.3	58	58.6	85	45.2
Subjective ability to work [2]						
Able to work	57	52.8	46	46.9	87	46.8
Unable to work	51	47.2	52	53.1	99	53.2

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder; [1] $p < 0.001$, [2] $p = 0.614$ (Chi-square test (between-diagnostic-group comparison))

Table 17. Logistic regression analysis of clinical correlates for objective and subjective ability to work within diagnostic groups (Study IV).

	SSA (n = 113)		BD (n = 99)		DD (n = 188)	
	B	Sig.	B	Sig.	B	Sig.
Objective work status						
Age	.03	.623	.28	**.002**	.05	.238
Age at onset	-.30	.155	-.21	**.009**	-.06	.120
Number of hospitalizations	.06	**.019**	.77	**.005**	.43	**.013**
BDI	.01	.906	.04	.461	.03	.172
OASIS	.25	.451	.04	.700	.06	.288
GSE	-.36	**.026**	-.08	.198	.02	.578
SDS (except "work" item)	0.43	**.031**	.17	**.005**	.14	**<.001**
Subjective ability to work						
Age	.05	**.037**	.02	.560	.03	.399
Age at onset	-.01	.698	.02	.622	.05	.130
Number of hospitalizations	.14	.516	.82	**.009**	.16	.329
BDI	.09	**.005**	.13	**.023**	.10	**<.001**
OASIS	.03	.657	.11	.300	.08	.144
GSE	-.01	.838	-.07	.232	-.06	.165
SDS (except "work" item)	.07	.121	.23	**.002**	.22	**<.001**

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

BDI = Beck Depression Inventory score; OASIS = Overall Anxiety Severity and Impairment Scale score; GSE = General Self-Efficacy scale score; SDS = Sheehan Disability Scale score ("work" item excluded)

6 DISCUSSION

Anxiety symptoms and harmful substance use were common across major mental disorders, with some inter-group differences. In particular, of all patients, those with schizophrenia or schizoaffective disorders experienced less anxiety and smoked more often, while subjects with bipolar disorder had the highest rate of alcohol consumption. Comorbid anxiety strongly loaded onto the internalizing domain, and substance use was associated with anxiety and poor adherence to treatment. Non-adherence was affected by hospital setting. Furthermore, recurrent psychiatric hospitalizations were associated with poor objective work status, while current depressive symptoms contributed to self-reported functional impairment. The main results were in line with the primary hypothesis, although findings regarding the effect of hospital setting on non-adherence and the impact of psychiatric hospitalizations on work status were somewhat unexpected.

6.1 STUDY I: ANXIETY SYMPTOMS IN MAJOR MOOD AND SCHIZOPHRENIA SPECTRUM DISORDERS

Severe anxiety was a common condition across the heterogeneous group of mood and schizophrenia spectrum disorders. Although the current study comprised anxiety symptoms, their proportions were similar to lifetime prevalence rates of comorbid anxiety disorders in previous reports (Brown et al., 2001; Achim et al., 2011; Pavlova et al., 2015).

As the vast majority of all patients, despite a principal diagnosis, experienced also clinically significant depressive symptoms, a high degree of anxiety could be partly explained by the phenomenon of internalization and a general temporal covariation of affective symptoms (Krueger, 1999; Hettema, 2008; Kendler et al., 2011; Kessler et al., 2011; Eaton et al., 2013; Melartin et al., 2014). The loading of the internalizing domain was, naturally, stronger in patients with mood disorders, as they reportedly suffered from significantly more severe anxiety than those with SSA. Regarding schizophrenia spectrum disorders, anxiety often emerges as a reaction to florid positive symptoms (Braga et al., 2013), but this mechanism probably did not play a substantial role in SSA patients, as most of them were outpatients, and thus, in relatively stable condition.

Another significant difference in patterns of anxiety was less prominent anxiety-related avoidance behaviour in patients with SSA than in patients with mood disorders. This may be related to negative symptoms, making patients with schizophrenia emotionally numb and somewhat indifferent to anxiety-provoking situations (Foussias et al., 2014). Moreover, SSA patients are exposed to such situations less frequently due to their general withdrawal from social roles (Konstantakopoulos et al., 2011; Hansen et al., 2013; Reddy et al., 2014).

Anxiety was not only highly prevalent across major mental disorders, but also associated with similar background factors. Of these, severe depressive symptoms and high neuroticism were the strongest correlates with anxiety, indicating that internalization is significant at the syndromal level. This phenomenon also appeared in all-variables regression analysis, where neuroticism in SSA patients was associated with comorbid anxiety symptoms as strongly as in DD patients, but not at all in BD patients. Neuroticism in this case seems to be an independent trigger of a cascade of affective symptoms beyond the domain of internalizing disorders, thus possibly also in schizophrenia spectrum disorders.

In addition to the strongest correlation of anxiety with symptoms of depression and neuroticism, associations were found also for self-efficacy and symptoms of borderline personality within all diagnostic groups, and for early trauma and distress in patients with mood disorders. These findings are generally in line with the literature. First, several studies have found low self-efficacy to be a significant factor in development, severity, and treatment of anxiety disorders (Richards et al., 2002; Gallagher et al., 2013). Results of the current study suggest a similar contribution to comorbid anxiety as a continuum as well. Second, anxiety symptoms are highly prevalent (up to 90%) in borderline personality disorder (Zanarini et al., 1998; Grant et al., 2008). Finally, numerous studies suggest an association between experienced childhood trauma and mood and schizophrenia spectrum disorders (Weber et al., 2008; Hovens et al., 2012; Larsson et al., 2013). Moreover, early trauma is related to a higher level of neuroticism (Roy, 2002; McFarlane et al., 2005), so traumatic experiences could potentially contribute to comorbid anxiety as a distal cause as well as a neuroticism-mediated condition.

Overall, the similarity of correlates of anxiety symptoms across different diagnostic groups suggests that anxiety could be a non-aligned condition rather than a direct consequence of the primary psychiatric pathology. However, primary pathophysiological mechanisms are likely engaged in comorbid anxiety more strongly in mood disorders, as anxiety was more severe in this group relative to SSA.

6.2 STUDY II: PSYCHOACTIVE SUBSTANCE USE IN SPECIALIZED PSYCHIATRIC CARE PATIENTS

The literature on substance use in clinical samples is extensive. The comorbidity rate of mental disorders and SUD has been estimated to be 19.5-25.0% (Melartin et al., 2002; Mantere et al., 2004; Ringen et al., 2008), and the proportion of SUD in this study corresponds to these findings. Regarding disorder-specific prevalence of substance use, the most common view is that among major mood and schizophrenia spectrum disorders, bipolar patients have the highest prevalence of SUDs (exceeding 60%), with alcohol consumption predominating (Regier et al., 1990, McElroy et al., 2001; Grant et al., 2005). The current study also demonstrated that SUDs and self-reported hazardous or harmful alcohol use emerge more often in subjects with BD. In contrast, in line with earlier reports (Ringen et al., 2008; Nesvåg et al., 2015), patients with SSA used non-alcohol drugs more often than their mood-disordered counterparts. In addition, smoking emerged more often in the SSA group, similarly to the findings on the highest (up to 70%) smoking prevalence in schizophrenia patients among the major psychiatric disorders (Lawrence et al., 2009; Dickerson et al., 2013; Smith et al., 2014; Jackson et al., 2015).

The overall rate of daily smoking in this specialized care study (~40%) is consistent with the prevalence for the general population worldwide (30-67%) (Grant et al., 2004; Lawrence et al., 2009; Smith et al., 2014). However, noting that only 30% of all patients in this study reported no history of smoking, the nicotine use is even more severe than in the general Finnish population, exceeding it by 2-3 times (27% in men and 19% in women) (Borodulin et al., 2015). Such a figure highlights that despite the availability of treatment methods (Tidey et al., 2015) smoking cessation among psychiatric patients remains insufficient, which affects the metabolism of psychiatric medication (Desai et al., 2001) and leads to tremendous somatic health consequences. Furthermore, heavy smoking accompanies substance use and dual diagnoses (Poirier et al., 2002; Holma et al., 2013; Smith et al., 2014), as was also found here.

Hazardous alcohol use was associated with severe symptoms of anxiety and borderline personality and low conscientiousness. Such findings were hardly surprising and supported the hypothesis of the current study, also being consistent with the postulations of many authors of a strong co-occurrence of alcohol use with anxiety symptoms (Kushner et al., 2000; Lai et al., 2015) and borderline personality disorder (Trull et al., 2010; Tromko et al., 2014; Grant et al., 2015). The association of a lower prevalence of hazardous alcohol use with the personality trait of conscientiousness likely represents the protective

effect of this trait (Donadon & Osório, 2016). Surprisingly, alcohol use was not related to high neuroticism, which is the only S5 personality trait responsible for the highest comorbidity rates of both internalizing (e.g. anxiety) and externalizing (e.g. substance use) disorders (Khan et al., 2005; Krueger & Markon, 2006).

Interestingly, although AUDIT-positive patients obtained high scores in all three AUDIT domains, they did not have any clinical diagnosis of AUD, assuming that the real prevalence of this diagnosis among AUDIT-positive patients was probably higher. Such discordance is likely to reflect a relatively common phenomenon of underestimation of substance abuse by patients (Devaux & Sassi, 2016) and, more importantly, by clinicians as well (Oiesvold et al., 2013). A clinician-related underestimation could result from many factors, such as insufficient systematic screening of substance use (Yoast et al., 2008) and occasionally missing the substance use-related data in medical records (Miller, 2002), hindering retrospective SUD diagnosis. Furthermore, general stigmatization of substance use often affects health care professionals (Crisp et al., 2000; Keyes et al., 2010), decreasing awareness of substance use problems. As a result, less than 30% of SUD patients receive proper treatment (Grant et al., 2009; Grant et al., 2015).

Overall, the majority of all patients had a diagnosed substance use disorder, hazardous alcohol use, or smoked daily. Substance abuse and smoking were common and interrelated, thus highlighting the clustering of hazardous lifestyles.

6.3 STUDY III: SELF-REPORTED TREATMENT ADHERENCE AMONG PSYCHIATRIC IN- AND OUTPATIENTS

Most patients reported positive attitudes towards any form of treatment and regular use of their medication without any difference between or within diagnostic groups. In turn, more than half of inpatients of all groups reported never attending outpatient visits, while in outpatients this figure did not exceed 11%. It is noteworthy that the majority of inpatients have utilized specialized psychiatric care for years, and thus, the proportion of non-adherent inpatients cannot be explained by their being treated for the first time. The substantial role of treatment setting in non-adherence was also demonstrated in regression analysis. However, the relationships between adherence to outpatient care and hospital treatment is more likely bidirectional. Hospitalization is naturally associated with a more severe

course of illness, which in some studies has been considered as a contributor to weak treatment adherence (Holma et al., 2010; Leclerc et al., 2013; Arvilommi et al., 2014). On the other hand, non-involvement in outpatient care results in insufficient treatment of mental disorders, leading to hospitalization (Grinshpoon et al., 2011).

Beyond these disease-related factors, sometimes attendance of outpatient visits is restricted by the health care system *via* high cost or deficient availability of such treatment forms (Saxena et al., 2007; Malowney et al., 2015). However, specialized psychiatric care patients of the Helsinki region do have the opportunity for regular and free-of-charge outpatient care. It is worth mentioning that separating psychiatric care and services for treatment of substance abuse, which is true also in Finland, reduces the availability of psychiatric treatment for patients with substance use comorbidity.

In line with earlier reports demonstrating a substantial impact of substance use on poor adherence to psychiatric treatment (Demyttenaere, 2003; Holma et al., 2010; Leclerc et al., 2013; Czobor et al., 2015), the current study found substance use disorder to be a strong contributor to non-adherence to outpatient visits. Along with disorder-related elements, this relationship is likely to include other domains. In addition to the obstacles from the health care system mentioned above, patients with substance abuse might experience both self-stigmatization (Fung et al., 2008) and stigma by health care professionals (Room, 2005; Keyes et al., 2010), which could lead to feeble treatment alliance and poor treatment adherence.

Regarding psychopharmacotherapy, most patients were positive about it and 71.7-83.7% of all patients reported regular use of medication. While previous studies have found self-reported adherence to psychopharmacotherapy (Rettenbacher et al., 2004; Holma et al., 2010; Arvilommi et al., 2014; De las Cuevas & Penate, 2015) to be 52.5-77.9%, objectively measured (serum levels, pill counts, etc.) compliance in usually lower, ranging from 34% to 50% (Leclerc et al., 2013; Yalcin-Siedentopf et al., 2014; Sajatovic et al., 2015). Therefore, self-reported measurements are not the most reliable, instead merely reflecting tendencies in overall compliance (Jónsdóttir et al., 2010). Medical adherence issues could be better detected with objective methods, increasing the efficacy of relapse prevention and mitigating the need for hospital treatment (Velligan et al., 2009; Yalcin-Siedentopf et al., 2014).

Interestingly, in all diagnostic groups the proportion of non-adherent SUD patients was higher among inpatients than outpatients. In view of the fact that irrespective of treatment setting all patients had a long-term mental care history, there was probably a group of SUD patients that neglected outpatient

care and utilized only psychiatric hospital services. Although this group is relatively small, it is likely to produce therapeutic challenges and to be at a high risk of negative outcome. Both poor adherence and substance abuse worsen the course of mental disorders (relapses, lack of remission) (Marder, 2003; Weiden et al., 2004; Kessler et al., 2005a) and intense suicidal behaviour (Meehan et al., 2006; Yuodelis-Flores & Ries, 2015), thus contributing to premature mortality in psychiatric patients compared with the general population (Wahlbeck et al., 2011; Walker et al., 2015). Moreover, inadequate outpatient treatment causes accumulating health and social problems, which result in often prolonged hospital treatment, increasing the costs of health care (Svarstad et al., 2001; Weiden et al., 2004).

Overall, regardless of the principal disorder, patients likely have a positive attitude towards treatment and intend to use their medication. Efforts should be directed to maintaining these positive factors during the treatment process.

6.4 STUDY IV: LEVEL OF FUNCTIONING, PERCEIVED WORK ABILITY, AND WORK STATUS AMONG PSYCHIATRIC PATIENTS WITH MAJOR MENTAL DISORDERS

The perceived level of functioning measured with the Sheehan Disability Scale was poor across all diagnostic groups, being lowest in patients with depression. This finding are somewhat contrary to earlier reports (mostly comparing functioning between only two major mental disorders) that describe substantial functional impairment in patients with bipolar disorder relative to patients with depression (van der Voort et al., 2015), or in patients with schizophrenia relative to patients with bipolar disorder (Bowie et al., 2010; Simonsen et al., 2010). Moreover, some studies with patients with mood and schizophrenia spectrum disorders failed to postulate principle diagnosis as a predictor of functional outcome, referring rather to neuropsychological mechanisms (Lee et al., 2013), or found that patients with bipolar disorders were the most functionally stable (Lee et al., 2015).

However, noting that DD patients reported the most severe depressive symptoms and the symptoms were associated with disability in all diagnostic groups in regression analysis, the highest subjective functional impairment in DD group could be interpreted through the affective domain. Depressive symptoms are a key element of poor psychosocial functioning in mood disorders (Rosa et al., 2008; Goldberg & Harrow, 2011; Gutierrez-Rojas et al., 2011; van der Voort et al., 2015; Hendriks et al., 2015), and especially negative self-referential thinking in depression (Disner et al., 2011) biases the

perception of functioning. In schizophrenia spectrum disorders, affective symptoms impair functioning as a secondary condition, while some negative symptoms, such as anhedonia, may overlap with those of depression (Braga et al., 2013; Johnson et al., 2014; Harvey, 2014; Sönmez et al., 2016).

Overall, our findings emphasize the importance of detection and proper treatment of affective symptoms in promoting functional recovery.

While perceived functioning was impaired in all patients, differences in work status were more significant, with a markedly low employment rate (5.3%) of SSA patients relative to the rates of 29.3% in BD and 33% in DD patients. Interestingly, despite DD patients obtaining the highest SDS scores, they were still the most employed group of all, likely reflecting a common subjective underestimation of functional level compared with objective assessment (Zimmerman et al., 2012; Pranjic & Males-Bilic, 2014;).

Many authors have demonstrated the impact of a long-term and severe course of disease on withdrawal from the labour force due to disability pension in schizophrenia spectrum disorders (Alptekin et al., 2005; Johnson et al., 2014), bipolar disorder (Arvilommi et al., 2015), and depression (Rytsälä et al., 2007; Holma et al., 2012). The results of regression analysis in the present study are in line with these findings, as both pensioning due to disability and being on sick leave were associated with repeated hospitalizations. Thus, the need for hospitalization likely reflects the overall severity, chronicity, and recurrent course of the principal mental disorder, which jointly lead to disability pension.

Along with number of hospitalizations, the SDS-measured functional impairment was another correlate of work disability in all patients. While studies on this topic differ by methodology and functioning assessment tools, the general assumption is that unfavourable employment outcome is partly predicted also by low perceived functioning (Razzano et al., 2005; Catty et al., 2008; Depp et al., 2012; Holma et al., 2012; Arvilommi et al., 2015). However, as “work” domain was excluded from overall SDS in regression analysis, the present study highlights the importance of perceived impaired functioning in areas of life, other than work, for retaining occupational roles.

One of the most notable findings of this study was the substantial gap between current labour status (5.3%) and subjective work ability (52.8%) in SSA patients. Such discrepancy reflects the general phenomenon of higher than clinician-assessed estimation of functional level (Oorschot et al., 2012) and quality of life (Bengtsson-Tops et al., 2005; Hayhurst et al., 2014) by patients with schizophrenia spectrum disorder due to their low insight and their

neurocognitive and, to some extent, negative symptoms. Furthermore, despite perceived disability, patients with severe mental illness (including schizophrenia spectrum disorders) still strongly desire to work (Tsang et al., 2010), likely having different frame of reference for judging their functioning. Both subjective and objective aspects of functioning are important in assessment of disability in patients with schizophrenia spectrum disorders (Harvey, 2014).

Relative to the SSA group, work status and subjective work ability were much more strongly interrelated in patients with mood disorders. Their level of self-reported work ability was, nevertheless, slightly higher than their vocational status, probably due to more prompt syndromal than functional remission (van der Voort et al., 2015).

Regarding the correlates of perceived work ability, the most consistent finding across all groups was the association of subjective work disability with current depressive symptoms. Thus, careful recognition and proper treatment of affective symptoms regardless of principal psychopathology are important for enhancing a patient´s motivation and engagement in rehabilitation programmes, thus promoting the return to work.

6.5 STRENGTHS AND LIMITATIONS

The main strength of the study was the determination of the characteristics of comorbid anxiety symptoms and substance use as well as the profile of treatment adherence and functional level simultaneously in schizophrenia spectrum, bipolar, and depressive disorders within a relatively large (N = 400) specialized care sample. A fairly comprehensive exploration of these parameters was enabled by using a broad spectrum of self-report scales (including the relatively novel OASIS).

The specific strength of the study on adherence to treatment (Study III) was its comparison within in- and outpatients as well as the detailed investigation of compliance with outpatient visits, which is often beyond the focus of related studies. The study on level of functioning (Study IV) comprised both objective and subjective measures of ability to work, enabling investigation of their consistency.

Several limitations of the study also warrant discussion. First, the study included a long survey and was conducted within a busy routine clinical practice, which, along with losing participants for technical reasons, resulted

in the relatively low response rate of 33%. Nonetheless, register-based analysis of representativeness demonstrated no difference from the patients of participating organizations by gender or age. Moreover, other demographic characteristics of patients in this study were consistent with those of the representative screening-based Vantaa Depression Study and Jorvi Bipolar Study in the same catchment area (Melartin et al., 2002; Mantere et al., 2004). However, the proportion of patients with disability pension was 18-19% higher in this study than elsewhere (Holma et al., 2012; Arvilommi et al., 2015). In addition to the generally low response rate, in Study IV, findings on correlates of work status in the SSA group should be interpreted with caution due to the low number (n=6) of subjects remaining at work.

Second, neither principal clinical diagnoses nor substance use disorder diagnoses were based on structured patient interviews, but were carefully validated by the authors by re-examining all available medical records. It is also noteworthy that patients´ diagnoses were initially set within specialized psychiatric care by psychiatrists and residents, thus assuming high validity. However, the possibility that medical records lack important information remains, potentially leading to well-acknowledged problem of mis- or underdiagnostics and a gap between the validity of diagnostics made by the clinician and the researcher (Moilanen et al., 2003; Mantere et al., 2004; Perälä et al., 2007).

Third, the present study included mostly self-reported measurements, with only a few objective variables. For instance, Study I lacked interview-based measures of anxiety symptoms and Study II substance use-related laboratory tests. Moreover, no objective information on attendance of outpatient treatment or medication use was collected for Study III. Study IV comprised data on labour status only from medical records (using these as the sole measure of objective ability to work), not, for example, from the Finnish Social Insurance Institution or other official registers. Also, cognitive profile as an important predictor of functional outcome (Lee et al., 2015) was not assessed here.

Fourth, self-reported measurements could be affected by recall bias (Liu et al., 2013), impairing their validity in statistical analyses. Furthermore, due to various patient- and disease-related factors, some patients could under- or overestimate their symptoms (Zimmerman et al., 2012; Oorschot et al., 2012), which is especially true for illicit substance use (Devaux & Sassi, 2016), and their adherence to psychiatric treatment.

Fifth, no conclusions on causal inferences or temporal variations between clinical and functional parameters could be drawn because of the cross-sectional study design.

7 CONCLUSIONS AND CLINICAL IMPLICATIONS

This study demonstrated that a high proportion of patients with major mood or schizophrenia spectrum disorders experience frequent and severe anxiety symptoms. As a strong co-incidence of symptoms representing negative affect is a well-established phenomenon, our findings were expected for patients with bipolar and depressive disorder. Such a high degree of perceived anxiety in patients with schizophrenia spectrum disorders was, however, somewhat surprising, although these patients did report anxiety less often than their mood-disordered peers. In addition, anxiety-related avoidance behaviour emerged less often in the SSA group, suggesting some phenomenological heterogeneity in comorbid anxiety profile, despite the overall similarity of its characteristics and background factors. Thus, in line with the literature, anxiety symptoms were strongly related to both concurrent presence of depressive symptoms and personality characteristics, particularly high neuroticism, regardless of the principal diagnosis. These results emphasize the importance of careful recognition and treatment of comorbid anxiety, which is especially true for the group of patients with schizophrenia spectrum disorders. In addition to general awareness of this condition in mood disorders, these patients are usually active in reporting depressive and anxiety symptoms and receive treatment effective for both of them. By contrast, in patients with schizophrenia negative affect may be masked by positive symptoms or functional impairment, and go unnoticed.

Along with comorbid anxiety, harmful substance use and smoking were common and interrelated, highlighting the clustering of hazardous lifestyles. As expected, prevalences of SUD diagnoses and self-reported alcohol use were greater in men than in women, and in bipolar patients than in other major mental disorders. By contrast, smoking was more common in SSA patients than in their affective disorder counterparts. Smoking cessation should, thus, be targeted, especially in schizophrenia spectrum disorders, as, in addition to general health adverse effects, nicotine use affects the metabolism of antipsychotic medication. Most of the patients with self-reported hazardous or harmful alcohol consumption did not have a clinical diagnosis of AUD, assuming that substance use disorders often go undiagnosed and, therefore, untreated. Alcohol use, but not smoking, was associated with symptoms of anxiety, borderline personality disorder, and low conscientiousness. Overall, while these variations may be useful for selective preventive interventions, there is a need for large-scale targeted preventive and treatment efforts

focusing on various types and stages of harmful substance use among psychiatric patients.

As with comorbid clinical features, the profile of adherence to psychiatric treatment was generally similar in patients with schizophrenia or schizoaffective disorder, bipolar disorder, and depression. In particular, patients reported high motivation and positive attitude both towards psychiatric medication and outpatient care. However, self-reported adherence to outpatient visits was significantly lower in current inpatients than in outpatients. Substance use disorders also strongly contributed to non-adherence, with the most significant impact in inpatients. Thus, to ensure proper psychiatric treatment, it is important to recognize harmful substance use and detect adherence issues irrespective of the primary psychopathology in every treatment setting, but especially among inpatients. Furthermore, following patient-centred principles of treatment and using motivational techniques with assistance of family members and relatives (e.g. shared decision-making, adherence therapy) might be beneficial in enhancing treatment compliance (Joosten et al., 2008; Borchers, 2014, Chien et al., 2015). Moreover, substance use-related non-adherence to treatment could be diminished by close collaboration between psychiatric care and substance abuse services.

As the present study was performed within specialized psychiatric care, the participants presumably suffered from a more severe course of principal disorders than patients treated in primary care. Moreover, as demonstrated in Studies I and II, levels of comorbid anxiety and substance use were also substantially high. Most likely, the combination of these factors resulted in the marked disability and withdrawal from the labour force seen in Study IV. Among all groups, perceived functional impairment and work disability were associated with current depressive symptoms, while objective work status reflected a severe course of illness, represented by number of preceding psychiatric hospitalizations. Among patients with mood disorders, objective and subjective indicators of ability to work are largely concordant, but among those with schizophrenia or schizoaffective disorder they are commonly contradictory. Such discordance highlights that the work status of patients with schizophrenia spectrum disorders is a multifactorial issue depending not only on the illness itself but also on the context (social support, health care system, rehabilitation, etc.). Strong efforts are needed for developing employment programmes for these patients.

8 IMPLICATIONS FOR FUTURE RESEARCH

With the growing costs and burden of mental disorders, the need to understand the clinical and functional features of psychiatric diseases spreads far beyond the medical and theoretical realms. As scientific importance of dimensional approach of diagnostic and investigation rapidly expands, there is a need in cross-diagnostic studies, methodologically similar to those of current thesis. However, more studies with pre-defined measures are required to enhance the response rate, and hence, the representativeness of the study sample. Subjective evaluations by patients should be validated and compared with objective measurements (researcher's assessment of diagnosis, treatment adherence, and functional level). In addition, covering the general population and patients throughout the health care pathway (i.e. from those with less severe disorders treated in primary health care to those in specialized psychiatric care) would give a more detailed understanding of the relationships of current symptoms and syndromes with a range of clinical and functional parameters. Verification of risk factors, predictors, or mediators for psychopathology and level of adherence and functioning, naturally, requires prospective studies.

REFERENCES

Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. Int Rev Psychiatry. 2010; 22(5):417-28.

Achim AM, Maziade M, Raymond E, Olivier D, Merette C, Roy MA. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. Schizophr Bull. 2011; 37(4):811–821.

Addington J, Liu L, Buchy L, Cadenhead KS, Cannon TD, Cornblatt BA, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Bearden CE, Mathalon DH, McGlashan TH. North American Prodrome Longitudinal Study (NAPLS 2): The Prodromal Symptoms. J Nerv Ment Dis. 2015; 203(5):328-35.

Agustí AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J. 2003; 21(2):347-60.

Ahmed AO, Strauss GP, Buchanan RW, Kirkpatrick B, Carpenter WT. Are Negative Symptoms Dimensional or Categorical? Detection and Validation of Deficit Schizophrenia With Taxometric and Latent Variable Mixture Models. Schizophr Bull. 2015; 41(4):879-91.

Alonso J, Lépine JP; ESEMeD/MHEDEA 2000 Scientific Committee. Overview of key data from the European Study of the Epidemiology of Mental Disorders (ESEMeD). J Clin Psychiatry. 2007; 68 Suppl 2:3-9.

Alonso J, Petukhova M, Vilagut G, Chatterji S, Heeringa S, Üstün TB, Alhamzawi AO, Viana MC, Angermeyer M, Bromet E, Bruffaerts R, de Girolamo G, Florescu S, Gureje O, Haro JM, Hinkov H, Hu CY, Karam EG, Kovess V, Levinson D, Medina-Mora ME, Nakamura Y, Ormel J, Posada-Villa J, Sagar R, Scott KM, Tsang A, Williams DR, Kessler RC. Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. Mol Psychiatry. 2011; 16(12):1234-46.

Alptekin K, Erkoc S; Gogus AK; Kultur S; Mete L; Ucok A; Yazici KM. Disability in schizophrenia: clinical correlates and prediction over 1-year follow-up. Psychiatry Res. 2005; 135 (2):103-111.

American psychiatric Association, Academy of Psychosomatic Medicine. Dissemination of integrated care within adult primary care settings. The collaborative care model. Report 2016.

Angst J, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res. 2005; 9(3):279-300.

Arbuckle R, Frye MA, Brecher M, Paulsson B, Rajagopalan K, Palmer S, Degl' Innocenti A. The psychometric validation of the Sheehan Disability Scale (SDS) in patients with bipolar disorder. Psychiatry Res. 2009; 165(1-2):163-74.

Arvilommi P, Suominen K, Mantere O, Valtonen H, Leppamaki S, Isometsa E. Predictors of long-term work disability among patients with type I and II bipolar disorder: a prospective 18-month follow-up study. Bipolar Disord. 2015; 17 (8):821-835.

Arvilommi P, Suominen K, Mantere O, Leppämäki S, Valtonen H, Isometsä E. Predictors of adherence to psychopharmacological and psychosocial treatment in bi polar I or II disorders - an 18-month prospective study. J Affect Disord. 2014; 155:110-7.

Babor TF, Saunders J, Grant M. AUDIT: The Alcohol Use Disorder Identification Test: Guidelines for Use in Primary Health Care. World Health Organization. Geneva, Switzerland. 1992.

Bahorik AL, Eack SM. Examining the course and outcome of individuals diagnosed with schizophrenia and comorbid borderline personality disorder. Schizophr Res. 2010; 124(1-3):29-35.

Baldwin DS, Allgulander C, Bandelow B, Ferre F, Pallanti S. An international survey of reported prescribing practice in the treatment of patients with generalised anxiety disorder. World J Biol Psychiatry. 2012; 13(7):510-6.

Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015; 17(3):327-35

Baryshnikov I, Aaltonen K, Koivisto M, Näätänen P, Karpov B, Melartin T, Heikkinen M, Ketokivi M, Joffe G, Isometsä E. Differences and overlap in self-reported symptoms of bipolar disorder and borderline personality disorder. Eur Psychiatry. 2015; 30(8):914-9.
Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4:561-571.

Bengtsson-Tops A, Hansson L, Sandlund M, Bjarnason O, Korkeila J, Merinder L, Nilsson L, Sørgaard KW, Vinding HR, Middelboe T. Subjective versus interviewer assessment of global quality of life among persons with schizophrenia living in the community: a Nordic multicentre study. Qual Life Res. 2005; 14(1):221-9.

Bjelland I, Lie SA, Dahl AA, Mykletun A, Stordal E, Kraemer HC. A dimensional versus a categorical approach to diagnosis: anxiety and depression in the HUNT 2 study. Int J Methods Psychiatr Res. 2009; 18(2):128-37.

Bolton JM, Robinson J, Sareen J. Self-medication of mood disorders with alcohol and drugs in the in the National Epidemiologic Survey on Alcohol and Related Conditions. J Affect Disord. 2009; 115(3):367-75.

Borchers P. "Issues like this have an impact": the need-adapted treatment of psychosis and the psychiatrist's inner dialogue. Doctoral dissertation. University of Jyväskylä, 2014.

Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, Männistö S, Salomaa V, Sundvall J, Puska P. Forty-year trends in cardiovascular risk factors in Finland. European Journal of Public Health. 2015; 25(3):539-46.

Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. Am J Psychiatry. 2000; 157(12):1925-32.

Bourne C, Aydemir Ö, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JT, Clark L, Cubukcuoglu Z, Dias VV, Dittmann S, Ferrier IN, Fleck DE, Frangou S, Gallagher P, Jones L, Kieseppä T, Martínez-Aran A, Melle I, Moore PB, Mur M, Pfennig A, Raust A, Senturk V, Simonsen C, Smith DJ, Bio DS, Soeiro-de-Souza MG, Stoddart SD, Sundet K, Szöke A, Thompson JM, Torrent C, Zalla T, Craddock N, Andreassen OA, Leboyer M, Vieta E, Bauer M, Worhunsky PD, Tzagarakis C, Rogers RD, Geddes JR, Goodwin GM.
Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individualpatient data meta-analysis. Acta Psychiatr Scand. 2013; 128(3):149-62.

Bower P, Gilbody S, Richards D, Fletcher J, Sutton A. Collaborative care for depression in primary care. Making sense of a complex intervention: systematic review and meta-regression. Br J Psychiatry. 2006; 189:484-93.

Bowie CR, Depp C, McGrath JA, Wolyniec P, Mausbach BT, Thornquist MH, Luke J, Patterson TL, Harvey PD, Pulver AE. Prediction of real-world functional disability in chronic mental disorders: a comparison of schizophrenia and bipolar disorder. Am J Psychiatry. 2010; 167(9):1116-1124.

Bowie CR, Twamley EW, Anderson H, Halpern B, Patterson TL, Harvey PD. Self-assessment of functional status in schizophrenia. J Psychiatr Res. 2007; 41(12):1012-8.

Brady KT, Sinha R. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. Am J Psychiatry. 2005; 162(8):1483-93.

Braga RJ, Reynolds GP, Siris SG. Anxiety comorbidity in schizophrenia. Psychiatry Res. 2013; 210(1):1-7.

Bragdon LB, Diefenbach GJ, Hannan S, Tolin DF. Psychometric properties of the Overall Anxiety Severity and Impairment Scale (OASIS) among psychiatric outpatients. J Affect Disord. 2016; 201:112-5.

Brown TA, Campbell LA, Lehman CL, Grisham JR, Mancill RB. Current and Lifetime Comorbidity of the DSM-IV Anxiety and Mood Disorders in a Large Clinical Sample. J Abnorm Psychol. 2001; 110(4):585-599.

Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull. 2009; 35(2):383-402.

Bystritsky A, Kerwin L, Niv N, Natoli JL, Abrahami N, Klap R, Wells K, Young AS. Clinical and subthreshold panic disorder. Depress Anxiety. 2010; 27(4):381-9.

Bäuml J, Froböse T, Kraemer S, Rentrop M, Pitschel-Walz G. Psychoeducation: a basic psychotherapeutic intervention for patients with schizophrenia and their families. Schizophr Bull. 2006;32 Suppl 1:1-9.

Campbell-Sills L, Norman SB, Craske MG, Sullivan G, Lang AJ, Chavira DA, Bystritsky A, Sherbourne C, Roy-Byrne P, Stein MB. Validation of a brief measure of anxiety-related severity and impairment: The Overall Anxiety Severity and Impairment Scale (OASIS). J Affect Disord. 2009; 112(1-3):92–101.

Cardno AG, Rijsdijk FV, Sham PC, Murray RM, McGuffin P. A twin study of genetic relationships between psychotic symptoms. Am J Psychiatry. 2002; 159: 539–545

Cassano G.B., Pini S., Saettoni M., Rucci P., Dell`Osso L. Occurrence and Clinical Correlates of Psychiatric Comorbidity in Patients With Psychotic Disorders. Journal Clin Psych. 1998; 59: 60 – 68.

Catty J, Lissouba P, White S, Becker T, Drake RE, Fioritti A, Knapp M, Lauber C, Rössler W, Tomov T, van Busschbach J, Wiersma D, Burns T; EQOLISE Group. Predictors of employment for people with severe mental illness: results of an international six-centrerandomised controlled trial. Br J Psychiatry. 2008; 192(3):224-31.

Chien WT, Mui JH, Cheung EF, Gray R. Effects of motivational interviewing-based adherence therapy for schizophrenia spectrum disorders: a randomized controlled trial. Trials. 2015;16:270.

Cheniaux E, Landeira-Fernandez J, Lessa-Telles L, Lessa JLM, Dias A, Duncan T, Versiani M. Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. J Affect Disord. 2008; 106(3):209–17.

Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. 2014; 13(2):153-60.

Clark LA, Watson D, Reynolds S. Diagnosis and classification of psychopathology: challenges to the current system and future directions. Annu Rev Psychol. 1995; 46:121-53.

Clemente AS, Diniz BS, Nicolato R, Kapczinski FP, Soares JC, Firmo JO, Castro-Costa É. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. Rev Bras Psiquiatr. 2015; 37(2):155-61.

Colom F, Vieta E, Tacchi MJ, Sánchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. Bipolar Disord. 2005; Suppl 5:24-31.

Comer JS, Blanco C, Hasin DS, Liu S-M, Grant BF, Turner JB, Olfson M. Health-related quality of life across the anxiety disorders. J Clin Psychiatry. 2011; 72(1):43–50.

Coodin S, Staley D, Cortens B, Desrochers R, McLandress S. Patient factors associated with missed appointments in persons with schizophrenia. Can J Psychiatry. 2004; 49(2):145-8.

Cooper C, Carpenter I, Katona C, et al. The AdHOC study of older adults' adherence to medication in 11 countries. Am J Geriatr Psychiatry. 2005;13:1067–76.

Costa, PT., McCrae, RR. 1992. NEO PI-R professional manual. Odessa, FL: Psychological Assessment Resources.

Crisp AH, Gelder MG, Rix S, Meltzer HI, Rowlands OJ. Stigmatisation of people with mental illnesses. Br J Psychiatry 2000; 177:4-7.

Cuijpers P, Schoevers RA. Increased mortality in depressive disorders: a review. Curr Psychiatry Rep. 2004; 6(6):430-7.

Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013; 14:126.

Czobor P, Van Dorn RA, Citrome L, Kahn RS, Fleischhacker WW, Volavka J. Treatment adherence in schizophrenia: a patient-level meta-analysis of combined CATIE and EUFEST studies. Eur Neuropsychopharmacol. 2015; 25(8):1158-66.

Dawe S, Seinen A, Kavanagh D. An examination of the utility of the AUDIT in people with schizophrenia. J Stud Alcohol. 2000; 61(5):744-50.

Dawson DA, Goldstein RB, Grant BF. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: a 3-year follow-up. Alcohol Clin Exp Res. 2007; 31(12):2036-45.

De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, Detraux J, Gautam S, Möller HJ, Ndetei DM, Newcomer JW, Uwakwe R, Leucht S. Physical illness in patients with severe mental disorders. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011; 10(1):52-77.

De Las Cuevas C, Penate W, Sanz EJ. The relationship of psychological reactance, health locus of control and sense of self-efficacy with adherence to treatment in psychiatric outpatients with depression. BMC psychiatry. 2014; 14:324

De Las Cuevas C, Peñate W. Explaining pharmacophobia and pharmacophilia in psychiatric patients: relationship with treatment adherence. Hum Psychopharmacol. 2015; 30(5):377-83.

De Las Cuevas C, Peñate W. Validation of the General Self-Efficacy Scale in psychiatric outpatient care. Psicothema. 2015; 27(4):410-5.

de Moor MH, van den Berg SM, Verweij KJ, Krueger RF, Luciano M, Arias Vasquez A, Matteson LK, Derringer J, Esko T,Amin N, Gordon SD, Hansell NK, Hart AB, Seppälä I, Huffman JE, Konte B, Lahti J, Lee M, Miller M, Nutile T, Tanaka T, Teumer A, Viktorin A, Wedenoja J,Abecasis GR, Adkins DE, Agrawal A, Allik J, Appel K, Bigdeli TB, Busonero F, Campbell H, Costa PT, Davey Smith G, Davies G, de Wit H, Ding J, Engelhardt BE, Eriksson JG, Fedko IO, Ferrucci L, Franke B, Giegling I, Grucza R, Hartmann AM, Heath AC, Heinonen K, Henders AK, Homuth G, Hottenga JJ, Iacono WG,Janzing J, Jokela M, Karlsson R, Kemp JP, Kirkpatrick MG, Latvala A, Lehtimäki T, Liewald DC, Madden PA, Magri C, Magnusson PK, Marten J, Maschio A,Medland SE, Mihailov E, Milaneschi Y, Montgomery GW, Nauck M, Ouwens KG, Palotie A, Pettersson E, Polasek O, Qian Y, Pulkki-Råback L, Raitakari OT,Realo A, Rose RJ, Ruggiero D, Schmidt CO, Slutske WS, Sorice R, Starr JM, St Pourcain B, Sutin AR, Timpson NJ, Trochet H, Vermeulen S, Vuoksimaa E,Widen E, Wouda J, Wright MJ, Zgaga L, Porteous D, Minelli A, Palmer AA, Rujescu D, Ciullo M, Hayward C, Rudan I, Metspalu A, Kaprio J, Deary IJ, Räikkönen K, Wilson JF, Keltikangas-Järvinen L, Bierut LJ, Hettema JM, Grabe HJ, van Duijn CM, Evans DM, Schlessinger D, Pedersen NL, Terracciano A, McGue M,Penninx BW, Martin NG, Boomsma DI. Meta-analysis of Genome-wide Association Studies for Neuroticism, and the Polygenic Association With Major Depressive Disorder. JAMA Psychiatry. 2015; 72(7):642-50.

Dell'Aglio JC Jr, Basso LA, Argimon II, Arteche A. Systematic review of the prevalence of bipolar disorder and bipolar spectrum disorders in population-based studies. Trends Psychiatry Psychother. 2013; 35(2):99-105.

Demyttenaere K. Risk factors and predictors of compliance in depression. Eur Neuropsychopharmacol. 2003; 13 Suppl 3:S69-75.

Depp CA, Mausbach BT, Bowie C, Wolyniec P, Thornquist MH, Luke JR, McGrath JA, Pulver AE, Harvey PD, Patterson TL. Determinants of occupational and residential functioning in bipolar disorder. J Affect Disord. 2012; 136(3):812-8.

Depp CA, Mausbach BT, Eyler LT, Palmer BW, Cain AE, Lebowitz BD, Patterson TL, Jeste DV. Performance-based and subjective measures of functioning in middle-aged and older adults with bipolar disorder. J Nerv Ment Dis. 2009;197(7):471-5.
Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. CNS Drugs 2001; 15(6):469-94.

Devaux M, Sassi F. Social disparities in hazardous alcohol use: self-report bias may lead to incorrect estimates. Eur J Public Health. 2016; 26(1):129-34.

Dickerson F, Stallings CR, Origoni AE, Vaughan C, Khushalani S, Schroeder J, Yolken RH. Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999-2011. Psychiatric Services 2013; 64(1):44-50.

Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci. 2011; 12(8):467-77.

Donadon MF, Osório FL. Personality traits and psychiatric comorbidities in alcohol dependence. Brazilian Journal of Medical Biological Researh 2016; 49(1):e5036.

Durand D, Strassnig M, Sabbag S, Gould F, Twamley EW, Patterson TL, Harvey PD. Factors influencing self-assessment of cognition and functioning in schizophrenia: implications for treatment studies. Eur Neuropsychopharmacol. 2015; 25(2):185-91.

Eaton NR, Krueger RF, Markon KE, Keyes KM, Skodol AE, Wall M, Hasin DS, Grant BF. The structure and predictive validity of the internalizing disorders. J Abnorm Psychol. 2013; 122(1): 86-92.

El-Mallakh RS, Hollifield M. Comorbid anxiety in bipolar disorder alters treatment and prognosis. Psychiatr Q. 2008; 79(2):139-150.

Eranti SV, MacCabe JH, Bundy H, Murray RM. Gender difference in age at onset of schizophrenia: a meta-analysis. Psychol Med. 2013;43(1):155-67.

Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E. Functional impairment in the remission phase of bipolar disorder. Bipolar Disord. 2005; 7 (3):281-285.

Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr Bull. 2009; 35(3):528-48.

Fazzino TL, Rose GL, Burt KB, Helzer JE. Comparison of categorical alcohol dependence versus a dimensional measure for predicting weekly alcohol use in heavy drinkers. Drug Alcohol Depend. 2014; 136:121-6.

Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis. 1970; 23(7):455-68.

Fergusson DM, Boden JM, Horwood LJ. Tests of causal links between alcohol abuse or dependence and major depression. Arch Gen Psychiatry. 2009; 66(3):260-6.

Ferrari AJ, Norman RE, Freedman G, Baxter AJ, Pirkis JE, Harris MG, Page A, Carnahan E, Degenhardt L, Vos T, Whiteford HA. The burden attributable to mental and substance use disorders as risk factors for suicide: findings from the Global Burden of Disease Study 2010. PLoS One. 2014; 9(4):e91936.

Few LR, Grant JD, Trull TJ, Statham DJ, Martin NG, Lynskey MT, Agrawal A. Genetic variation in personality traits explains genetic overlap between borderline personality features and substance use disorders. Addiction 2014; 109(12):2118-27.

Fisher M, Loewy R, Hardy K, Schlosser D, Vinogradov S. Cognitive interventions targeting brain plasticity in the prodromal and early phases of schizophrenia. Annu Rev Clin Psychol. 2013; 9:435-63.

Fodor GJ, Kotrec M, Bacskai K, et al. Is interview a reliable method to verify the compliance with antihypertensive therapy? An international central-European study. J Hypertens. 2005;23:1261–6.

Forbush KT, Watson D.The structure of common and uncommon mental disorders. Psychol Med. 2013; 43(1):97-108.

Foussias G, Agid O, Fervaha G, Remington G. Negative symptoms of schizophrenia: Clinical features, relevance to real world functioning and specificity versus other CNS disorders. Eur Neuropsychopharmacol. 2014; 24 (5):693 – 709.

Fraley RC, Waller NG, Brennan KA. An item response theory analysis of self-report measures of adult attachment. J Pers Soc Psychol. 2000; 78:350 – 365.

Frasch K, Larsen JI, Cordes J, Jacobsen B, Wallenstein Jensen SO, Lauber C, Nielsen JA, Tsuchiya KJ, Uwakwe R, Munk-Jørgensen P, Kilian R, Becker T. Physical illness in psychiatric inpatients: comparison of patients with and without substance use disorders. International Journal of Social Psychiatry 2013; 59(8):757-64.

Fung KM, Tsang HW, Corrigan PW. Self-stigma of people with schizophrenia as predictor of their adherence to psychosocial treatment. Psychiatr Rehabil J. 2008; 32(2):95-104.

Gallagher MW, Payne LA, White KS, Shear KM, Woods SW, Gorman JM, Barlow DH. Mechanisms of change in cognitive behavioral therapy for panic disorder: The unique effects of self-efficacy and anxiety sensitivity. Behav Res Ther. 2013; 51 (11):767 – 777.

Gibson S, Brand SL, Burt S, Boden ZV, Benson O. Understanding treatment non-adherence in schizophrenia and bipolar disorder: a survey of what service users do and why. BMC Psychiatry. 2013; 13:153.

Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. Arch Intern Med. 2006; 166(21):2314-21.

Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry. 2004; 161(4):692-9.

Glasheen C, Hedden SL, Forman-Hoffman VL, Colpe LJ. Cigarette smoking behaviors among adults with serious mental illness in a nationally representative sample. Annals of Epidemiology 2014; 24(10):776-80.

Goldberg JF, Harrow M. A 15-year prospective follow-up of bipolar affective disorders: comparisons with unipolar nonpsychotic depression. 2011; 13 (2):155-163.

Goldner EM, Hsu L, Waraich P, Somers JM. Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature. Can J Psychiatry. 2002; 47(9):833-43.

Gould F, McGuire LS, Durand D, Sabbag S, Larrauri C, Patterson TL, Twamley EW, Harvey PD. Self-assessment in schizophrenia: Accuracy of evaluation of cognition and everyday functioning. Neuropsychology. 2015; 29(5):675-82.

Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet. 2016; 387(10027):1561-72

Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, Smith SM, Dawson DA, Pulay AJ, Pickering RP, Ruan WJ. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2008; 69 (4):533 – 545.

Grant BF, Goldstein RB, Chou SP, Huang B, Stinson FS, Dawson DA, Saha TD, Smith SM, Pulay AJ, Pickering RP, Ruan WJ, Compton WM. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. Mol Psychiatry. 2009; 14(11):1051-66.

Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, Pickering RP, Ruan WJ, Smith SM, Huang B, Hasin DS. Epidemiology of DSM-5 Alcohol Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015; 72(8):757-66.

Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. Archives of General Psychiatry 2004; 61(11):1107-15.

Grant BF, Saha TD, Ruan WJ, Goldstein RB, Chou SP, Jung J, Zhang H, Smith SM, Pickering RP, Huang B, Hasin DS. Epidemiology of DSM-5 Drug Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions-III. JAMA Psychiatry. 2016, 73(1):39-47.

Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, Huang B. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2005; 66(10):1205-15.

Grief SN. Nicotine dependence: health consequences, smoking cessation therapies, and pharmacotherapy. Prim Care. 2011; 38(1):23-39.

Griffith JW, Zinbarg RE, Craske MG, Mineka S, Rose RD, Waters AM, Sutton JM. Neuroticism as a common dimension in the internalizing disorders. Psychol Med. 2010; 40 (7):1125-1136.

Grinshpoon A, Lerner Y, Hornik-Lurie T, Zilber N, Ponizovsky AM. Post-discharge contact with mental health clinics and psychiatric readmission: a 6-month follow-up study. Isr J Psychiatry Relat Sci. 2011; 48(4):262-7.

Gutierrez-Rojas L, Jurado D, Gurpegui M. Factors associated with work, social life and family life disability in bipolar disorder patients. Psychiatry Res. 2011; 186 (2-3):254-260.

Haller H, Cramer H, Lauche R, Gass F, Dobos GJ. The prevalence and burden of subthreshold generalized anxiety disorder: a systematic review. BMC Psychiatry. 2014;14:128.

Hansen CF, Torgalsboen AK, Rossberg JI, Romm KL, Andreassen OA, Bell MD, Melle I. Object relations, reality testing, and social withdrawal in schizophrenia and bipolar disorder. J Nerv Ment Dis. 2013; 201(3):222 – 225.

Harford TC, Chen CM, Saha TD, Smith SM, Ruan WJ, Grant BF. DSM-IV personality disorders and associations with externalizing and internalizing disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Psychiatr Res. 2013; 47(11):1708-16.

Harrow M, Grossman LS, Herbener ES, Davies EW. Ten-year outcome: patients with schizoaffective disorders, schizophrenia, affective disorders and mood-incongruent psychotic symptoms. Br J Psychiatry. 2000; 177:421-6.

Harvey PD, Paschall G, Depp C. Factors influencing self-assessment of cognition and functioning in bipolar disorder: a preliminary study. Cogn Neuropsychiatry. 2015; 20(4):361-71.

Harvey PD, Velligan DI, Bellack AS. Performance-based measures of functional skills: usefulness in clinical treatment studies. Schizophr Bull. 2007; 33(5):1138-48.

Harvey PD. Disability in schizophrenia: contributing factors and validated assessments. J Clin Psychiatry. 2014; 75 (Suppl 1):15-20.

Hasin D, Trautman K, Miele G, Samet S, Smith M, Endicott J. Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. Am J Psychiatry 1996; 153:1195–1201.

Hawton K, Casañas I Comabella C, Haw C, Saunders K. Risk factors for suicide in individuals with depression: a systematic review. J Affect Disord. 2013; 147(1-3):17-28

Hayhurst KP; Massie JA; Dunn G; Lewis SW; Drake RJ. Validity of subjective versus objective quality of life assessment in people with schizophrenia. BMC Psychiatry. 2014; 14:365

Hearnshaw H, Lindenmeyer A. What do we mean by adherence to treatment and advice for living with diabetes? A review of the literature on definitions and measurements. Diabet Med. 2006 Jul;23(7):720-8.

Hendriks SM; Spijker J; Licht CM; Hardeveld F; de Graaf R; Batelaan NM; Penninx BW; Beekman AT. Long-term work disability and absenteeism in anxiety and depressive disorders. J Affect Disord. 2015; 178:121-130.

Hettema JM. What is the genetic relationship between anxiety and depression? Am J Med Genet C Semin Med Genet. 2008; 14 (2):140-6.

Hjorthøj C, Østergaard ML, Benros ME, Toftdahl NG, Erlangsen A, Andersen JT, Nordentoft M. Association between alcohol and substance use disorders and all-cause and cause-specific mortality inschizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study. Lancet Psychiatry. 2015; 2(9):801-8.

Hoertel N, Le Strat Y, Angst J, Dubertret C. Subthreshold bipolar disorder in a U.S. national representative sample: prevalence, correlates and perspectives for psychiatric nosography. J Affect Disord. 2013; 146(3):338-47.

Holma IA, Holma KM, Melartin TK, Rytsala HJ, Isometsa ET. A 5-year prospective study of predictors for disability pension among patients with major depressive disorder. Acta Psychiatr Scand. 2012; 125 (4):325-334.

Holma IA, Holma KM, Melartin TK, Isometsä ET. Treatment attitudes and adherence of psychiatric patients with major depressive disorder: a five-year prospective study. J Affect Disord. 2010;127(1-3):102–12.

Holma IA, Holma KM, Melartin TK, Ketokivi M, Isometsä ET. Depression and smoking: a 5-year prospective study of patients with major depressive disorder. Depression and Anxiety 2013; 30(6):580-8.

Hovens JG, Giltay EJ, Wiersma JE, Spinhoven P, Penninx BW, Zitman FG. Impact of childhood life events and trauma on the course of depressive and anxiety disorders. Acta Psychiatr Scand. 2012; 126(3):198-207.

Huppert JD, Weiss KA, Lim R, Pratt S, Smith TE. Quality of life in schizophrenia: contributions of anxiety and depression. Schizophr Res. 2001; 51 (2-3):171-180.

IBM SPSS Statistics for Windows, Version 22.0. Released 2013. Armonk, NY: IBM Corp.

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167(7):748-51.

Inskip HM, Harris EC, Barraclough B. Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry. 1998; 172:35-7.

Ishak WW, Balayan K, Bresee C, Greenberg JM, Fakhry H, Christensen S, Rapaport MH. A descriptive analysis of quality of life using patient-reported measures in major depressive disorder in a naturalistic outpatient setting. Qual Life Res. 2013; 22(3):585-96.
Isometsä E. Suicidal behaviour in mood disorders--who, when, and why? Can J Psychiatry. 2014; 59(3):120-30.

Ito M, Oe Y, Kato N, Nakajima S, Fujisato H, Miyamae M, Kanie A, Horikoshi M, Norman SB. Validity and clinical interpretability of Overall Anxiety Severity And Impairment Scale (OASIS). J Affect Disord. 2015; 170:217-24.

Jablensky, A. (2009). Course and outcome of schizophrenia and their prediction. In M.G. Gelder, N. Andreasen, J.J. Lopez-Ibor Jr & J.R. Geddes (Eds), New Oxford Textbook of Psychiatry (2nd ed.) (pp. 568 – 578). Oxford: Oxford University Press.

Jackson JG, Diaz FJ, Lopez L, de Leon J. A combined analysis of worldwide studies demonstrates an association between bipolar disorder and tobacco smoking behaviors in adults. Bipolar Disorders 2015; 17(6):575-97.

Jacobi F, Höfler M, Siegert J, Mack S, Gerschler A, Scholl L, Busch MA, Hapke U, Maske U, Seiffert I, Gaebel W, Maier W, Wagner M, Zielasek J, Wittchen HU. Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: the MentalHealth Module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). Int J Methods Psychiatr Res. 2014; 23(3):304-19.

Jager M, Haack S, Becker T, Frasch K. Schizoaffective disorder–an ongoing challenge for psychiatric nosology. Eur Psychiatry 2011;26:159–165.

Janssen I, Krabbendam L, Bak M, Hanssen M, Vollebergh W, de Graaf R, van Os J. Childhood abuse as a risk factor for psychotic experiences. Acta Psychiatr Scand. 2004;109(1):38-45.

Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008; 4(1):269-86.

Johnson S; Sathyaseelan M; Charles H; Jacob KS. Predictors of disability: a 5-year cohort study of first-episode schizophrenia. Asian J Psychiatr. 2014; 9:45-50.

Jónsdóttir H, Opjordsmoen S, Birkenaes AB, et al. Medication adherence in outpatients with severe mental disorders: relation between self-reports and serum level. J Clin Psychopharmacol. 2010; 30(2):169-75.

Joosten EA, DeFuentes-Merillas L, de Weert GH, Sensky T, van der Staak CP, de Jong CA. Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status. Psychother Psychosom. 2008; 77(4):219-26.

Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry. 2003; 60(3):261-9.

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002; 59(6):530-7.

Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, Veijola J, Miettunen J. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013;39(6):1296-306.

Karsten J, Penninx BW, Verboom CE, Nolen WA, Hartman CA. 2013. Course and risk factors of functional impairment in subthreshold depression and anxiety. Depress Anxiety. 2013; 30(4): 386-94.

Karsten J., Nolen W.A., Penninx B.W., Hartman C.A., 2011. Subthreshold anxiety better defined by symptom self-report than by diagnostic interview. Journal of Affective Disorders; 129(1-3):236-43.

Kendler KS, Aggen SH, Knudsen GP, Røysamb E, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. Am J Psychiatry. 2011; 168(1):29-39.

Kendler KS, Gardner CO, Fiske A, Gatz M. Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. Arch Gen Psychiatry. 2009; 66(8):857-63.

Kessler RC, Angermeyer M, Anthony JC, DE Graaf R, Demyttenaere K, Gasquet I, DE Girolamo G, Gluzman S, Gureje O, Haro JM, Kawakami N, Karam A, Levinson D, Medina Mora ME, Oakley Browne MA, Posada-Villa J, Stein DJ, Adley Tsang CH, Aguilar-Gaxiola S, Alonso J, Lee S, Heeringa S, Pennell BE, Berglund P, Gruber MJ, Petukhova M, Chatterji S, Ustün TB. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007; 6(3):168-76.

Kessler RC, Avenevoli S, Costello EJ, Georgiades K, Green JG, Gruber MJ, He JP, Koretz D, McLaughlin KA, Petukhova M, Sampson NA, Zaslavsky AM, Merikangas KR. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. Arch Gen Psychiatry. 2012; 69(4):372-80.

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289(23):3095-105.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005a; 62(6):593-602.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005b; 62(6):617-27.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994; 51(1):8-19.

Kessler RC, Ormel J, Petukhova M, McLaughlin KA, Green JG, Russo LJ, Stein DJ, Zaslavsky AM, Aguilar-Gaxiola S, Alonso J, Andrade L, Benjet C, de Girolamo G, de Graaf R, Demyttenaere K, Fayyad J, Haro JM, Hu C, Karam A, Lee S, Lepine J-P, Matchsinger H, Mihaescu-Pintia C, Posada-Villa J, Sagar R, Üstün TB. Development of lifetime comorbidity in the WHO World Mental Health (WMH) Surveys. Arch Gen Psychiatry. 2011; 68(1):90–100.

Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen H -U. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorde rs in the United States. Int J Methods Psychiatr Res. 2012; 21(3):169-84.

Kessler RC. The costs of depression. Psychiatr Clin North Am. 2012; 35(1):1-14

Keyes KM, Hatzenbuehler ML, McLaughlin KA, Link B, Olfson M, Grant BF, Hasin D. Stigma and treatment for alcohol disorders in the United States. Am J Epidem. 2010; 172(12):1364-72.

Khan AA, Jacobson KC, Gardner CO, Prescott CA, Kendler KS. Personality and comorbidity of common psychiatric disorders. Br J Psychiatry. 2005; 186:190-6.

Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I, Conigliaro J, Haas GL. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord. 2004; 6(5):368-73.
Kilbourne AM, Reynolds CF 3rd, Good CB, Sereika SM, Justice AC, Fine MJ. How does depression influence diabetes medication adherence in older patients? Am J Geriatr Psychiatry. 2005 Mar; 13(3):202-10.

Kleinman L, Lieberman J, Dube S, Mohs R, Zhao Y, Kinon B, Carpenter W, Harvey PD, Green MF, Keefe RS, Frank L, Bowman L, Revicki DA. Development and psychometric performance of the schizophrenia objective functioning instrument: an

interviewer administered measure of function. Schizophr Res. 2009; 107(2-3):275–85.

Koivumaa-Honkanen H, Tuovinen TK, Honkalampi K, Antikainen R, Hintikka J, Haatainen K, Viinamäki H. Mental health and well-being in a 6-year follow-up of patients with depression: assessments of patients and clinicians. Soc Psychiatry Psychiatr Epidemiol. 2008; 43(9):688-96.

Konstabel K., Lönnqvist J.-E., Walkowitz G., Konstabel K., Verkasalo M. The 'Short Five' (S5): measuring personality traits using comprehensive single items. Eur J Pers. 2012; 26(1):13–29.

Konstantakopoulos G, Ploumpidis D, Oulis P, Patrikelis P, Soumani A, Papadimitriou GN, Politis AM. Apathy, cognitive deficits and functional impairment in schizophrenia. Schizophr Res. 2011. 133 (1-3):193 – 198.

Kooiman CG, Klaassens ER, van Heloma Lugt JQ, Kamperman AM. Psychometrics and validity of the Dutch Experiences in Close Relationships-Revised (ECR-r) in an outpatient mental health sample. J Pers Assess. 2013; 95(2):217-24.

Kraemer HC. Research Domain Criteria (RDoC) and the DSM--Two Methodological Approaches to MentalHealth Diagnosis. JAMA Psychiatry. 2015; 72(12):1163-4.

Kristjansson S, McCutcheon VV, Agrawal A, Lynskey MT, Conroy E, Statham DJ, Madden PA, Henders AK, Todorov AA, Bucholz KK, Degenhardt L, Martin NG, Heath AC, Nelson EC. The variance shared across forms of childhood trauma is strongly associated with liability for psychiatric and substance use disorders. Brain and Behavior 2016; 6(2): e00432.

Krueger RF, Caspi A, Moffitt TE, Silva PA. The structure and stability of common mental disorders (DSM-III-R): A longitudinal-epidemiological study. J Abnorm Psychol. 1998; 107(2): 216-227.

Krueger RF, McGue M, Iacono WG. The higher-order structure of common DSM mental disorders: internalization, externalization, and their connections to personality. Pers Invidid Dif. 2001; 30(7): 1245-1259.

Krueger RF, Markon KE, Patrick CJ, Iacono WG. Externalizing psychopathology in adulthood: a dimensional-spectrum conceptualization and its implications for DSM-V. J Abnorm Psychol. 2005; 114(4):537-50.

Krueger RF, Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. Annu Rev Clin Psychol. 2006; 2:111-33.

Krueger RF. The Structure of Common Mental Disorders. Arch Gen Psychiatry. 1999; 56 (10):921-926.

Kruijshaar ME, Barendregt J, Vos T, de Graaf R, Spijker J, Andrews G. Lifetime prevalence estimates of major depression: an indirect estimation method and a quantification of recall bias. Eur J Epidemiol. 2005; 20(1):103-11.

Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet. 2012; 17:379(9820):1045-55.

Kurtz MM, Olfson RH, Rose J. Self-efficacy and functional status in schizophrenia: relationship to insight, cognition and negative symptoms. Schizophr Res. 2013; 145(1-3):69-74.

Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. Clinical Psychology Review 2000; 20(2):149-71.

Kushner MG. Seventy-five years of comorbidity research. J Stud Alcohol Drugs Suppl. 2014; 75 Suppl 17:50-8.

Lai HM, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: A systematic review and meta-analysis. Drug Alcohol Dep. 2015; 154:1-13.

Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry. 2011;68(6):555-61.

Larsson S, Andreassen OA, Aas M, Røssberg JI, Mork E, Steen NE, Barrett EA, Lagerberg TV, Peleikis D, Agartz I, Melle I, Lorentzen S. High prevalence of childhood trauma in patients with schizophrenia spectrum and affective disorder. Compr Psychiatry. 2013; 54(2):123-127.

Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Annu Rev Clin Psychol. 2014; 10:425-48.

Lawrence D, Mitrou F, Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. BMC Public Health. 2009; 9:285.

Leclerc E, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J Affect Disord. 2013; 149(1-3):247-52.

Lee RS, Hermens DF, Naismith SL, Lagopoulos J, Jones A, Scott J, Chitty KM, White D, Robillard R, Scott EM, Hickie IB. Neuropsychological and functional outcomes in recent-onset major depression, bipolar disorder and schizophrenia-spectrum disorders: a longitudinal cohort study. Transl Psychiatry. 2015; 5:e555.

Lee RS, Hermens DF, Redoblado-Hodge MA, Naismith SL, Porter MA, Kaur M, White D, Scott EM, Hickie IB. Neuropsychological and socio-occupational functioning in young psychiatric outpatients: a longitudinal investigation. PLoS One. 2013; 8(3):e58176.

Leifker FR, Patterson TL, Heaton RK, Harvey PD. Validating measures of real-world outcome: the results of the VALERO expert survey and RAND panel. Schizophr Bull. 2011; 37(2):334-43.

Leon AC, Shear MK, Portera L, Klerman GL. Assessing impairment in patients with panic disorder: the Sheehan Disability Scale. Soc Psychiatry Psychiatr Epidemiol. 1992; 27(2):78-82.

Leuchter AF, Hunter AM, Tartter M, Cook IA. Role of pill-taking, expectation and therapeutic alliance in the placebo response in clinical trials for major depression. Br J Psychiatry. 2014;205(6):443-9.

Li TK. Quantifying the risk for alcohol-use and alcohol-attributable health disorders: present findings and future research needs. J Gastroenterol Hepatol. 2008; 23 Suppl 1:S2-8.

Liu X, Li L, Xiao J, Yang J, Jiang X. Abnormalities of autobiographical memory of patients with depressive disorders: a meta-analysis. Psychol Psychother. 2013; 86(4):353-73.

Lohoff FW. Overview of the genetics of major depressive disorder. Curr Psychiatry Rep. 2010; 12(6):539-46.
Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006; 367 (9524):1747-1757.

Luutonen S, Tikka M, Karlsson H, Salokangas RK. Childhood trauma and distress experiences associate with psychotic symptoms in patients attending primary and psychiatric outpatient care. Results of the RADEP study. Eur Psychiatry. 2013; 28(3):154-60.

Maisto SA, Carey MP, Carey KB, Gordon CM, Gleason JR. Use of the AUDIT and the DAST-10 to identify alcohol and drug use disorders among adults with a severe and persistent mental illness. Psychol Assess. 2000; 12(2):186-92.

Maj M, Pirozzi R, Formicola AM, Bartoli L, Bucci P. Reliability and validity of the DSM-IV diagnostic category of schizoaffective disorder: preliminary data. J Affect Disord 2000; 57:95–98.

Malhi GS, Green M, Fagiolini A, Peselow ED, Kumari V. Schizoaffective disorder: diagnostic issues and future recommendations. Bipolar Disord. 2008; 10(1 Pt 2):215-30.

Malowney M, Keltz S, Fischer D, Boyd JW. Availability of outpatient care from psychiatrists: a simulated-patient study in three U.S. cities. Psychiatr Serv. 2015; 66(1):94-6.

Mancuso SG, Morgan VA, Mitchell PB, Berk M, Young A, Castle DJ. A comparison of schizophrenia, schizoaffective disorder, and bipolar disorder: Results from the Second Australian national psychosis survey. J Affect Disord. 2015; 172:30-7

Mantere O, Melartin TK, Suominen K, Rytsala HJ, Valtonen HM, Arvilommi P, Leppamaki S, Isometsa ET. Differences in Axis I and II comorbidity between bipolar I and II disorders and major depressive disorder. J Clin Psychiatry. 2006; 67 (4):584 – 593.

Mantere O, Suominen K, Leppämäki S, Valtonen H, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). Bipolar Disorders 2004; 6(5):395-405.

Marder SR. Overview of partial compliance. J Clin Psychiatry. 2003; 64 Suppl 16:3-9.

Margolese HC, Malchy L, Negrete JC, Tempier R, Gill K. Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences. Schizophrenia Research. 2004; 67(2-3):157-66.
Markkula N, Suvisaari J, Saarni SI, Pirkola S, Peña S, Saarni S, Ahola K, Mattila AK, Viertiö S, Strehle J, Koskinen S, Härkänen T. Prevalence and correlates of major depressive disorder and dysthymia in an eleven-year follow-up – results from the Finnish Health 2011 Survey. J Affect Disord. 2015; 173:73-80.

Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology. 1998; 18:135–174.

Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry. 2004; 161(2):262-70.

Marwaha S, Johnson S. Schizophrenia and employment - a review. Soc Psychiatry Psychiatr Epidemiol. 2004; 39 (5):337-349.

Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006; 3(11):e442.

McElroy SL, Altshuler LL, Suppes T, Keck PE Jr, Frye MA, Denicoff KD, Nolen WA, Kupka RW, Leverich GS, Rochussen JR, Rush AJ, Post RM. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. American Journal of Psychiatry. 2001; 158(3):420-6.

McFarlane A, Clark CR, Bryant RA, Williams LM, Niaura R, Paul RH, Hitsman BL, Stroud L, Alexander DM, Gordon E. The impact of early life stress on psychophysiological, personality and behavioral measures in 740 non-clinical subjects. J Integr Neurosci. 2005; 4(1):27-40.

McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008; 30:67-76.

McGrath JJ. Myths and plain truths about schizophrenia epidemiology--the NAPE lecture 2004. Acta Psychiatr Scand. 2005; 111(1):4-11.

Meehan J, Kapur N, Hunt IM. Suicide in mental health in-patients and within 3 months of discharge. National clinical survey. Br J Psychiatry. 2006; 188:129-34.

Melartin T, Mantere O, Ketokivi M, Isometsä E. A prospective latent analysis study of Axis I psychiatric co-morbidity of DSM-IV major depressive disorder. Psychol Med. 2014; 44(5):949–959.
Melartin T, Häkkinen M, Koivisto M, Isometsä ET. Screening of psychiatric outpatients for borderline personality disorder with the McLeanScreening Instrument for Borderline Personality Disorder (MSI-BPD). Nord J Psychiatry. 2009; 63(6):475-9.

Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. J Clin Psychiatry. 2002; 63(2):126-34.

Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, Viana MC, Andrade LH, Hu C, Karam EG, Ladea M, Medina-Mora ME, Ono Y, Posada-Villa J, Sagar R, Wells JE, Zarkov Z. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011;68(3):241-51.

Merikangas KR, Lamers F. The 'true' prevalence of bipolar II disorder. Curr Opin Psychiatry. 2012; 25(1):19-23.

Miller PR. Inpatient diagnostic assessments: 3. Causes and effects of diagnostic imprecision. Psychiatry Research 2002; 111(2-3):191-7.

Miloyan B, Byrne GJ, Pachana NA. Threshold and Subthreshold Generalized Anxiety Disorder in Later Life. Am J Geriatr Psychiatry. 2015; 23(6): 633-641.

Moffitt TE, Caspi A, Taylor A, Kokaua J, Milne BJ, Polanczyk G, Poulton R. How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychol Med. 2010; 40(6):899-909.

Moilanen K, Veijola J, Läksy K, Mäkikyrö T, Miettunen J, Kantojärvi L, Kokkonen P, Karvonen JT, Herva A, Joukamaa M, Järvelin MR, Moring J, Jones PB, Isohanni M. Reasons for the diagnostic discordance between clinicians and researchers in schizophrenia in the Northern Finland 1966 Birth Cohort. Soc Psychiatry Psychiatr Epidemiol. 2003; 38(6):305-10.

Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007; 370(9590):851-8.

Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380 (9859):2197-2223.

Nardi AE, Nascimento I, Freire RC, de-Melo-Neto VL, Valença AM, Dib M, Soares-Filho GL, Veras AB, Mezzasalma MA, Lopes FL, de Menezes GB, Grivet LO, Versiani M. Demographic and clinical features of schizoaffective (schizobipolar) disorder--a 5-year retrospective study. Support for a bipolar spectrum disorder. J Affect Disord. 2005; 89(1-3):201-6.

Narvaez JM, Twamley EW, McKibbin CL, Heaton RK, Patterson TL. Subjective and objective quality of life in schizophrenia. Schizophr Res. 2008; 98(1-3):201-8.

National Epidemiologic Survey on Alcohol and Related Conditions. J Affect Disord. 2009; 115:367–375.

National Institute for Health and Welfare. Psychiatric specialist medical care 2015. Statistical Report 21/2016, 9.6.2017.

Nesvåg R, Knudsen GP, Bakken IJ, Høye A, Ystrom E, Surén P, Reneflot A, Stoltenberg C, Reichborn-Kjennerud T. Substance use disorders in schizophrenia, bipolar disorder, and depressive illness: a registry-based study. Soc Psychiatry Psychiatr Epidemiol 2015; 50(8):1267-76.

Nivoli AM, Pacchiarotti I, Rosa AR, Popovic D, Murru A, Valenti M, Bonnin CM, Grande I, Sanchez-Moreno J, Vieta E, Colom F. Gender differences in a cohort study of 604 bipolar patients: the role of predominant polarity. J Affect Disord. 2011; 133(3):443-9.

Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry. 2011; 68(10):1058-64.

Norman SB, Campbell-Sills L, Hitchcock CA, Sullivan S, Rochlin A, Wilkins KC, Stein MB. Psychometrics of a brief measure of anxiety to detect severity and impairment: The overall anxiety severity and impairment scale (OASIS). J Psychiatr Res. 2011; 45(2):262-268.

Norman SB, Cissell SH, Means-Christensen AJ, Stein MB. Development and validation of an Overall Anxiety Severity and Impairment Scale (OASIS). Depress Anxiety. 2006; 23(4):245–249.

Oiesvold T, Nivison M, Hansen V, Skre I, Ostensen L, Sørgaard KW. Diagnosing comorbidity in psychiatric hospital: challenging the validity of administrative registers. BMC Psychiatry. 2013; 13:13.

Oorschot M, Lataster T, Thewissen V, Lardinois M, van Os J, Delespaul PA, Myin-Germeys I. Symptomatic remission in psychosis and real-life functioning. Br J Psychiatry. 2012; 201 (3):215-220.
Ormel J, Jeronimus BF, Kotov R, Riese H, Bos EH, Hankin B, Rosmalen JG, Oldehinkel AJ. Neuroticism and common mental disorders: meaning and utility of a complex relationship. Clin Psychol Rev. 2013; 33(5):686-697.

Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016; 388(10039):86-97.

Pacek LR, Martins SS, Crum RM. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: results from a national sample. J Affect Disord. 2013;148:188–195.

Pagel T, Baldessarini RJ, Franklin J, Baethge C. Characteristics of patients diagnosed with schizoaffective disorder compared with schizophrenia and bipolar disorder. Bipolar Disord. 2013; 15(3):229-39.

Pallaskorpi S, Suominen K, Ketokivi M, Mantere O, Arvilommi P, Valtonen H, Leppämäki S, Isometsä E. Five-year outcome of bipolar I and II disorders: findings of the Jorvi Bipolar Study. Bipolar Disord. 2015; 17(4):363-74.

Pallaskorpi S, Suominen K, Ketokivi M, Valtonen H, Arvilommi P, Mantere O, Leppämäki S, Isometsä E. Incidence and predictors of suicide attempts in bipolar I and II disorders: A 5-year follow-up study. Bipolar Disord. 2017; 19(1):13-22.

Patterson P, Skeate A, Schultze-Lutter F, Graf von Reventlow H, Wieneke A, Ruhrmann S, Salokangas RKR. Birmingham: University of Birmingham, 2002.

Pavlova B, Perlis RH, Alda M, Uher R. Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry. 2015; 2(8):710-717.

Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci. 2008;9(12):947-57.

Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Härkänen T, Koskinen S, Lönnqvist J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry. 2007; 64(1):19-28.

Pinna F, Sanna L, Perra V, Pisu Randaccio R, Diana E, Carpiniello B; Cagliari Recovery Study Group. Long-term outcome of schizoaffective disorder. Are there any differences with respect to schizophrenia? Riv Psichiatr. 2014; 49(1):41-9.

Pirkola SP, Isometsä E, Suvisaari J, Aro H, Joukamaa M, Poikolainen K, Koskinen S, Aromaa A, Lönnqvist JK. DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population--results from the Health 2000 Study. Soc Psychiatry Psychiatr Epidemiol. 2005; 40(1):1-10.

Poirier MF, Canceil O, Baylé F, Millet B, Bourdel MC, Moatti C, Olié JP, Attar-Lévy D. Prevalence of smoking in psychiatric patients. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2002; 26(3):529-37.

Pranjic N, Males-Bilic L. Work ability index, absenteeism and depression among patients with burnout syndrome. Mater Sociomed. 2014; 26 (4):249-252.

Rantakallio P, Jones P, Moring J, Von Wendt L. Association between central nervous system infections during childhood and adult onset schizophrenia and other psychoses: a 28-year follow-up. Int J Epidemiol. 1997;26(4):837-43.

Razzano LA, Cook JA, Burke-Miller JK, Mueser KT, Pickett-Schenk SA, Grey DD, Goldberg RW, Blyler CR, Gold PB, Leff HS, Lehman AF, Shafer MS, Blankertz LE, McFarlane WR, Toprac MG, Ann Carey M. Clinical factors associated with employment among people with severe mental illness: findings from the employment intervention demonstration program. J Nerv Ment Dis. 2005; 193(11):705-13.

Reddy LF, Green MF, Rizzo S, Sugar CA, Blanchard JJ, Gur RE, Kring AM, Horan WP. Behavioral approach and avoidance in schizophrenia: An evaluation of motivational profiles. Schizophr Res. 2014; 159 (1):164 – 170.

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990; 264(19):2511-8.

Rettenbacher MA, Hofer A, Eder U, et al. Compliance in schizophrenia: psychopathology, side effects, and patients' attitudes toward the illness and medication. J Clin Psychiatry. 2004; 65(9):1211-8.

Richards D. Prevalence and clinical course of depression: a review. Clin Psychol Rev. 2011; 31(7):1117-25.

Richards JC, Richardson V, Pier C. The Relative Contributions of Negative Cognitions and Self-efficacy to Severity of Panic Attacks in Panic Disorder. Behav Change. 2002; 19(2):102 – 111.

Ringen PA, Lagerberg TV, Birkenaes AB, Engn J, Faerden A, Jónsdottir H, Nesvåg R, Friis S, Opjordsmoen S, Larsen F, Melle I, Andreassen OA. Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. Psycholog Medicine 2008; 38(9):1241-9.

Room R. Stigma, social inequality and alcohol and drug use. Drug Alcohol Rev. 2005; 24(2):143-55.

Rosa AR; Franco C; Martinez-Aran A; Sanchez-Moreno J; Reinares M; Salamero M; Arango C; Ayuso-Mateos JL; Kapczinski F; Vieta E. Functional impairment in patients with remitted bipolar disorder. Psychother Psychosom. 2008; 77 (6):390-392.

Roy A. Childhood trauma and neuroticism as an adult: possible implication for the development of the common psychiatric disorders and suicidal behavior. Psychol Med. 2002; 32 (8):1471-1474.

Rytsälä HJ, Melartin TK, Leskela US, Sokero TP, Lestela-Mielonen PS, Isometsa ET. Predictors of long-term work disability in Major Depressive Disorder: a prospective study. Acta Psychiatr Scand. 2007; 115 (3):206-213.

Saarni SI, Suvisaari J, Sintonen H, Pirkola S, Koskinen S, Aromaa A, Lönnqvist J. Impact of psychiatric disorders on health-related quality of life: general population survey. Br J Psychiatry. 2007; 190:326 – 332.

Sabaté E. Adherence to long-term therapies: evidence for action. World Health Organization; 2003.

Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007; 64(10):1123-31.

Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005; 2(5):e141.

Sajatovic M, Levin JB, Sams J, et al. Symptom severity, self-reported adherence, and electronic pill monitoring in poorly adherent patients with bipolar disorder. Bipolar Disord. 2015; 17(6):653-61.

Sansone RA, Sansone LA. Antidepressant adherence: are patients taking their medications? Innov Clin Neurosci. 2012;9(5-6):41-6.

Sarvet AL, Hasin D. The natural history of substance use disorders. Curr Opin Psychiatry. 2016; 29(4):250-7.

Saxena S, Thornicroft G, Knapp M, Whiteford H. Resources for mental health: scarcity, inequity, and inefficiency. Lancet. 2007; 370(9590):878-89.
Schaffer A, Isometsä ET, Tondo L, H Moreno D, Turecki G, Reis C, Cassidy F, Sinyor M, Azorin JM, Kessing LV, Ha K, Goldstein T, Weizman A, Beautrais A, Chou YH, Diazgranados N, Levitt AJ, Zarate CA Jr, Rihmer Z, Yatham LN. International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar Disord. 2015;17(1):1-16.

Schwarzer R, Jerusalem M. Generalized Self-Efficacy scale. In: Weinman J, Wright S, Johnston M. Measures in health psychology: A user's portfolio. Causal and control beliefs. Windsor, UK; 1995. p. 35-37.

Segarra R, Ojeda N, Zabala A, García J, Catalán A, Eguíluz JI, Gutiérrez M. Similarities in early course among men and women with a first episode of schizophrenia and schizophreniform disorder. Eur Arch Psychiatry Clin Neurosci. 2012; 262(2):95-105.

Senior V, Marteau TM, Weinman J. Self-reported adherence to cholesterol-lowering medication in patients with familial hypercholesterolaemia: the role of illness perceptions. Cardiovasc Drugs Ther. 2004;18:475–81

Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996; 11 Suppl 3:89-95.

Sheehan DV. The Anxiety Disease. New York, NY, USA: Charles Scribners Sons; 1983.

Shimada-Sugimoto M, Otowa T, Hettema JM. Genetics of anxiety disorders: Genetic epidemiological and molecular studies in humans. Psychiatry Clin Neurosci. 2015; 69(7):388-401.

Simonsen C; Sundet K; Vaskinn A; Ueland T; Romm KL; Hellvin T; Melle I; Friis S; Andreassen OA. Psychosocial function in schizophrenia and bipolar disorder: Relationship to neurocognition and clinical symptoms J Int Neuropsychol Soc. 2010; 16 (5):771-783, England.

Smith PH, Mazure CM, McKee SA. Smoking and mental illness in the US population. Tobacco Control 2014*;* 23:e147-e153.

Smoller JW, Ripke S, Lee PH, Neale B, Nurnberger JI, Santangelo S, et al. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013; 381(9875):1371-9.

Sönmez N; Rossberg JI; Evensen J; Barder HE; Haahr U; Ten Velden Hegelstad W; Joa I;Johannessen JO; Langeveld H; Larsen TK; Melle I; Opjordsmoen S; Rund BR; Simonsen E; Vaglum P; McGlashan T; Friis S. Depressive symptoms in first-episode psychosis: a 10-year follow-up study. Early Interv Psychiatry. 2016; 10 (3):227-233.

Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003; 60(12):1187-92.

Suominen K, Mantere O, Valtonen H, Arvilommi P, Leppämäki S, Paunio T, Isometsä E. Early age at onset of bipolar disorder is associated with more severe clinical features but delayed treatment seeking. Bipolar Disord. 2007; 9(7):698-705.

Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. Psychiatr Serv. 2001; 52(6):805-11.

Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, Malaspina D, Owen MJ, Schultz S, Tsuang M, Van Os J, Carpenter W. Definition and description of schizophrenia in the DSM-5. Schizophr Res. 2013; 150(1):3-10.

Taylor L, Faraone SV, Tsuang MT. Family, twin, and adoption studies of bipolar disease. Curr Psychiatry Rep. 2002; 4(2):130-3.

Tidey JW, Miller ME. Smoking cessation and reduction in people with chronic mental illness. BMJ 2015; 351:h4065.

Tienari P, Wynne LC, Sorri A, Lahti I, Läksy K, Moring J, Naarala M, Nieminen P, Wahlberg KE. Genotype-environment interaction in schizophrenia-spectrum disorder. Long-term follow-up study of Finnish adoptees. Br J Psychiatry. 2004;184:216-22.

Tomko RL, Trull TJ, Wood PK, Sher KJ. Characteristics of borderline personality disorder in a community sample: comorbidity, treatment utilization, and general functioning. Journal of Personality Disorders 2014; 28(5):734-50.

Trull TJ, Jahng S, Tomko RL, Wood PK, Sher KJ. Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substancedependence disorders. J Pers Disor 2010; 24(4):412-26

Tsai J, Rosenheck RA. Psychiatric comorbidity among adults with schizophrenia: a latent class analysis. Psychiatry Res. 2013; 210(1):16-20.

Tsang HW, Leung AY, Chung RC, Bell M, Cheung WM. Review on vocational predictors: a systematic review of predictors of vocational outcomes among individuals with schizophrenia: an update since 1998. Aust N Z J Psychiatry. 2010; 44 (6):495-504.

van Os J, Kapur S. Schizophrenia. Lancet. 2009; 374(9690):635-45.

van Os J, Jones PB. Neuroticism as a risk factor for schizophrenia. Psychol Med. 2001; 31 (6): 1129-1134.

van der Voort TY; Seldenrijk A; van Meijel B; Goossens PJ; Beekman AT; Penninx BW; Kupka RW. Functional versus syndromal recovery in patients with major depressive disorder and bipolar disorder. J Clin Psychiatry. 2015; 76 (6):e809-14.

Varela-Rey M, Woodhoo A, Martinez-Chantar ML, Mato JM, Lu SC. Alcohol, DNA methylation, and cancer. Alcohol Res. 2013; 35(1):25-35.

Veijola J; Guo JY; Moilanen JS; Jaaskelainen E; Miettunen J; Kyllonen M; Haapea M; Huhtaniska S; Alaraisanen A; Maki P; Kiviniemi V; Nikkinen J; Starck T; Remes JJ; Tanskanen P; Tervonen O; Wink AM; Kehagia A; Suckling J; Kobayashi H; Barnett JH; Barnes A; Koponen HJ; Jones PB; Isohanni M; Murray GK. Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. PLoS ONE. 2014; 9(7).

Velligan DI, Weiden PJ, Sajatovic M, et al.; Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009; 70 Suppl 4:1-46.

Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388(10053):1545-1602.

Wahlbeck K, Forsén T, Osmond C, Barker DJ, Eriksson JG. Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. Arch Gen Psychiatry. 2001 Jan;58(1):48-52.

Wahlbeck K, Westman J, Nordentoft M, Gissler M, Laursen TM. Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. Br J Psychiatry 2011; 199(6):453-8.

Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry. 2015; 72(4):334-41.
Wang J-C, Kapoor M, Goate AM. The Genetics of Substance Dependence. Annu Rev Genomics Hum Genet. 2012; 13: 241–261.

Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. Rev Bras Psiquiatr. 2013; 35(4):416-31.

Weaver T, Madden P, Charles V, Stimson G, Renton A, Tyrer P, Barnes T, Bench C, Middleton H, Wright N, Paterson S, Shanahan W, Seivewright N, Ford C. Comorbidity of Substance Misuse and Mental Illness Collaborative study team.

Comorbidity of substance misuse and mental illness in community mental health and substance misuse services. Br J Psychiatry 2003; 183:304-13.

Weber K, Rockstroh B, Borgelt J, Awiszus B, Popov T, Hoffmann K, Schonauer K, Watzl H, Pröpster K. Stress load during childhood affects psychopathology in psychiatric patients. BMC Psychiatry. 2008; 8:63.

Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among CaliforniaMedicaid patients with schizophrenia. Psychiatr Serv. 2004; 55(8):886-91.

Weiller E, Bisserbe JC, Maier W, Lecrubier Y. Prevalence and recognition of anxiety syndromes in five European primary care settings: a report from the WHO study on psychological problems in general health care. Br J Psychiatry Suppl. 1998; 34:18 – 23.

Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PLoS One. 2015; 10(2):e0116820.

WHO global report on trends in tobacco smoking 2000-2025. Geneva, 2015.

Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen H-C. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011; 21(9):655-679.

World Health Organization (WHO) The global burden of disease: 2004 update. Geneva: World Health Organization; 2008.

World Health Organization. International classification of disease, 10th ed., Geneva; 1992.
Wray NR et al., Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013; 45(9):984-94.

Yalcin-Siedentopf N, Wartelsteiner F, Kaufmann A, et al. Measuring adherence to medication in schizophrenia: the relationship between attitudes toward drug therapy and plasma levels of new-generation antipsychotics. Int J Neuropsychopharmacol. 2014; 18(5).

Yamauchi K, Aki H, Tomotake M, Iga J, Numata S, Motoki I, Izaki Y, Tayoshi S, Kinouchi S, Sumitani S, Tayoshi S, Takikawa Y, Kaneda Y, Taniguchi T, Ishimoto Y, Ueno S, Ohmori T. Predictors of subjective and objective quality of life in outpatients with schizophrenia. Psychiatry Clin Neurosci. 2008; 62(4):404-11.

Yoast RA, Wilford BB, Hayashi SW. Encouraging physicians to screen for and intervene in substance use disorders: obstacles and strategies for change. Journal of Addictive Disorders 2008; 27(3):77-97.

Yuodelis-Flores C, Ries RK. Addiction and suicide: A review. Am J Addict 2015; 24(2):98-104.

Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, Reynolds V. Axis I comorbidity of borderline personality disorder. Am J Psychiatry. 1998; 155 (12):1733 – 1739.

Zanarini MC, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J. A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). J Pers Disord. 2003; 17(6):568-573.

Zimmerman M, Martinez JA, Attiullah N, Friedman M, Toba C, Boerescu DA, Rahgeb M. Why do some depressed outpatients who are in remission according to the Hamilton Depression Rating Scale not consider themselves to be in remission? J Clin Psychiatry. 2012; 73 (6):790-795.

Zvolensky MJ, Taha F, Bono A, Goodwin RD. Big five personality factors and cigarette smoking: a 10-year study among US adults. Journal of Psychiatric Research 2015; 63:91-6.

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Original article

Anxiety symptoms in a major mood and schizophrenia spectrum disorders

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ABSTRACT

Background: Comorbid anxiety symptoms and disorders are present in many psychiatric disorders, but methodological variations render comparisons of their frequency and intensity difficult. Furthermore, whether risk factors for comorbid anxiety symptoms are similar in patients with mood disorders and schizophrenia spectrum disorders remains unclear.

Methods: The Overall Anxiety Severity and Impairment Scale (OASIS) was used to measure anxiety symptoms in psychiatric care patients with schizophrenia or schizoaffective disorder (SSA, $n = 113$), bipolar disorder (BD, $n = 99$), or depressive disorder (DD, $n = 188$) in the Helsinki University Psychiatric Consortium Study. Bivariate correlations and multivariate linear regression models were used to examine associations of depressive symptoms, neuroticism, early psychological trauma and distress, self-efficacy, symptoms of borderline personality disorder, and attachment style with anxiety symptoms in the three diagnostic groups.

Results: Frequent or constant anxiety was reported by 40.2% of SSA, 51.5% of BD, and 55.6% of DD patients; it was described as severe or extreme by 43.8%, 41.4%, and 41.2% of these patients, respectively. SSA patients were significantly less anxious ($P = 0.010$) and less often avoided anxiety-provoking situations ($P = 0.009$) than the other patients. In regression analyses, OASIS was associated with high neuroticism, symptoms of depression and borderline personality disorder and low self-efficacy in all patients, and with early trauma in patients with mood disorders.

Conclusions: Comorbid anxiety symptoms are ubiquitous among psychiatric patients with mood or schizophrenia spectrum disorders, and in almost half of them, reportedly severe. Anxiety symptoms appear to be strongly related to both concurrent depressive symptoms and personality characteristics, regardless of principal diagnosis.

1. Introduction

Anxiety symptoms are conceptualized as anxiety disorders (ADs) when they constitute specified syndromes and are intensive, recurrent, and impede an individual's psychosocial functioning [1]. ADs are the most common psychiatric conditions in the general population, with typical estimates for lifetime prevalence of 16–28% [2–5]. ADs also commonly co-occur with other psychiatric conditions. For instance, up to 38% of patients with schizophrenia [6], 45% of patients with bipolar disorder [7], and 73% of patients with depression [8] reportedly suffer from a lifetime comorbid AD(s). ADs impair quality of life and are associated with poorer prognosis and outcome of psychotic and affective disorders [9–13]. This is true also for comorbid subthreshold anxiety [14–16]. Thus, careful recognition and proper treatment of comorbid anxiety, either as diagnosable disorders or as subthreshold states, are important in clinical practice.

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Abundant literature on anxiety disorder comorbidity among patients with major mental disorders exists [6,17,18]. The majority of these studies have focused on the presence of specific comorbid disorders [19], rarely reporting on subthreshold anxiety symptoms, even if clinically relevant. Few studies on comorbid anxiety disorders or symptoms have included both uni- and bipolar mood as well as non-affective psychotic disorders, and methodological variations have rendered comparisons of the results difficult. Hence, it remains unclear whether prevalence of anxiety symptoms and their putative risk factors are similar in patients with schizophrenia or schizoaffective disorder (SSA), bipolar disorder (BD), and depressive disorder (DD).

Anxiety and depressive disorders constitute the main internalizing mental disorders [20,21], with a high level of temporal covariation [22]. Recent studies have found that bipolar disorder shares some etiological and pathogenetic connections with the internalizing domain as well [23,24]. The internalizing disorders are likely to share most of their genetic basis [25–27]. The personality trait of high neuroticism is the most significant risk factor for internalizing pathology [28,29] and a likely mediator of the underlying genetic diathesis for these disorders [30]. However, many other putative risk factors also contribute to the anxiety and depressive disorders. These factors include childhood and adolescence psychological trauma [31], low self-efficacy [32,33], borderline personality disorder [34], and negative experiences in close relationships [35]. Some findings indicate that the same factors could also affect the onset of schizophrenia and worsen its outcome [36–39]. However, whether similar covariation of depressive and anxiety symptoms exists and whether the same putative risk factors underlie anxiety in schizophrenia spectrum disorders and internalizing disorders remain unclear.

This study had both clinical and theoretical aims. The clinical aim was to compare the point prevalence of comorbid anxiety symptoms among psychiatric patients with depression, bipolar disorder, and schizophrenia or schizoaffective disorders. We hypothesized that the level of anxiety symptoms in patients with schizophrenia or schizoaffective disorder would be lower since, in contrast to mood disorders, these psychotic disorders are not diagnostically defined by the presence of negative affect as a central pathognomonic feature. The theoretical aim was to investigate the relationships of anxiety symptoms with neuroticism, depressive symptoms, and other putative risk factors. We expected that anxiety symptoms would show a clear association with these factors in patients with mood disorders, and explored whether the same relationships would apply to patients with schizophrenia spectrum disorders, in other words beyond the internalizing domain.

2. Methods

2.1. Setting

The current study was a part of the Helsinki University Psychiatric Consortium (HUPC) study performed in collaboration between the Faculty of Medicine, University of Helsinki; the Department of Psychiatry, Helsinki University Central Hospital; the Department of Health and the Mental Health Unit of the National Institute of Health and Welfare, Helsinki; the Department of Social Services and Health Care, Psychiatric Services, Helsinki; and the Department of Psychiatry, Helsinki City Health Department. The catchment area with 1,139,222 inhabitants in 2012 covered the metropolitan area of Helsinki, including the municipalities of Helsinki, Espoo, Vantaa, Kauniainen, Kerava, and Kirkkonummi. Specialized secondary mental health service is provided to these residents. The study was carried out in 10 community mental health centers, in 24 psychiatric inpatient units, in one day-care hospital, and in two residential communities. The HUPC study was approved by the Ethics Committee of Helsinki University Hospital and the pertinent institutional authorities.

2.2. Sampling

Stratified patient sampling was performed from 12 January 2011 to 20 December 2012. Patients were randomly drawn either by identifying all eligible patients on a certain day or week in a unit or from patient lists. Inclusion criteria were age from 18 to 64 years and provision of written informed consent. Patients with mental retardation, neurodegenerative disorders, and insufficient Finnish language skills were excluded. Of the 1361 eligible patients, 610 declined to participate and 304 were lost for other reasons. The final number of participants was 447, yielding a response rate of 33%. For the current study, patients with a principal diagnosis of anxiety disorder, eating disorder, neuropsychiatric disorder, or substance use disorder ($n = 47$) were excluded from the final analyses due to the low number of patients in each group. The total number of patients, thus, was 400.

2.3. Diagnostic assessment

Diagnostic assessments were made according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [40] following the principle of lifetime main diagnosis. The authors (K.A, I.B., M.K., and B.K.) verified the clinical diagnoses given by attending psychiatrists by re-examining information obtained from all available medical records. In cases of any diagnostic uncertainty, the senior research psychiatrists (G.J. and E.I.) were consulted. Altogether, 69 cases were consulted. According to the principal diagnosis, patients were divided into three diagnostic groups: schizophrenia or schizoaffective disorder (SSA, $n = 113$), bipolar disorder (BD, $n = 99$), and depressive disorder (DD, $n = 188$).

2.4. Measurement of symptoms and traits

Overall Anxiety Severity and Impairment Scale (OASIS) [41] is a brief, 5-item self-report questionnaire to assess severity and impairment associated with any anxiety disorder, multiple anxiety disorders, or subthreshold anxiety. The authors of the current article translated the OASIS into Finnish, which was then back translated into English and the translation revised in collaboration with the creator of OASIS, Dr. Sonya Norman. The questionnaire includes five questions regarding the frequency and severity of anxiety symptoms as well as anxiety-related avoidance behavior and decreased functioning at home/work/school and in social life. Responses range from zero (no anxiety or anxiety-related issues) to four (extreme anxiety and massive anxiety-related issues). A recommended cut-off score for screening of anxiety disorder is eight points [42]. Cronbach's alpha for OASIS in the total sample was 0.84, and specifically, 0.88 for SSA, 0.86 for BD, and 0.78 for DD patients, showing good internal consistency overall and in the subgroups.

Beck Depression Inventory (BDI) [43] is a 21-item self-report questionnaire for measuring the severity of depression symptoms. The "Short Five" (S5) [44] is a 60-item questionnaire constructed for measuring 30 facets of the Five-Factor Model identified by the NEO (Neuroticism-Extraversion-Openness) Personality Inventory. The current study used six items describing neuroticism (S5N). The S5N scale as well as the other four scales (Extraversion, Openness, Agreeableness, and Conscientiousness) showed good internal consistency (Cronbach's alpha for S5N see below, other values not shown). The Experiences in Close Relationships-Revised

questionnaire (ECR-R) [45] is a self-report 36-item measure of adult attachment style on anxiety and avoidance subscales. The General Self-Efficacy scale (GSE) [46] is a self-report 10-item instrument to assess perceived self-efficacy regarding stressful life events. The McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD, hereafter MSI) [47] is a self-report 10-item questionnaire to detect the possibility of borderline personality disorder (BPD). The Trauma and Distress Scale (TADS) [48,49] is a self-report 43-item scale for the assessment of early (childhood and early adulthood) traumatic experiences and distress. All of the scales had at least good internal consistency (Chronbach's alpha for BDI – 0.91; for S5N – 0.85; for ECR anxiety scale – 0.95 and avoidance scale – 0.97; for GSE – 0.93; for MSI – 0.92; and for TADS – 0.80).

2.5. Statistical analyses

The differences between nominal sociodemographic variables across diagnostic groups were explored with Chi-square test, and between continuous variables with the Kruskal–Wallis test. Nominal dichotomous variables, such as sex, presence or absence of children, education (primary or secondary and higher), smoking status, and care unit (in- or outpatients) were compared with mean OASIS scores using *t*-tests or Mann–Whitney *U*-tests; for marital status the Kruskal–Wallis test was used. The relationships between the OASIS and continuous variables (age, age of onset of illness, and duration of illness) were tested with bivariate correlation analysis. Age of onset and duration of illness were determined based on time of occurrence of the first symptoms reported by the patients. For investigation of the clinical hypothesis of the study, the differences between both the mean total scores and separate item scores of OASIS across the diagnostic groups the Kruskal–Wallis test was used. Bivariate correlation analysis (BCA; Spearman's coefficient) was used to estimate correlation of OASIS with BDI, S5N, MSI, GSE, TADS, and ECR anxiety and avoidance; analysis was performed for each group of patients separately. In order to test the theoretical hypothesis of the study, linear regression model was built to estimate the association between the OASIS (dependent variable) and measures correlated with it in BCA (independent variables) across all diagnostic groups. These measures were all of the above-mentioned variables, with the exception of ECR avoidance. In addition, sex and age were included in the analysis. Separate regression models were constructed for each diagnostic group. As additional analysis and partly to avoid the problem of multicollinearity, regression analysis was performed for all independent variables and then with BDI and S5N excluded one at a time and simultaneously. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences [50].

3. Results

3.1. Sociodemographic and background data

Table 1 shows the main sociodemographic characteristics of the sample. The patients were middle-aged and there was no significant difference in mean age between diagnostic groups ($P = 0.112$). The sex distribution differed markedly, with a preponderance of females in the DD and BD groups, but nearly equal distribution in the SSA group ($P < 0.001$). SSA patients had a family and children less often than BD and DD patients ($P < 0.001$). The proportion of childless patients in the DD group was higher than in the BD group. No significant differences in educational level or proportion of smokers were found. Of all the diagnostic groups, the SSA group had a highest proportion of inpatients.

Table 1
Sociodemographic and background characteristics of the sample.

	SSA		BD		DD		Total		*P*-value
	n	%	*n*	%	*n*	%	*n*	%	
Number	113	28.2	99	24.8	188	47.0	400	100.0	
Female	54	47.8	63	63.6	146	77.7	263	65.7	<0.001[a]
Marital status									<0.001[b]
Married	2	1.8	20	20.2	39	21.0	61	15.4	
Cohabitation	8	7.3	17	17.2	29	15.6	54	13.7	
Divorced	16	14.5	29	29.3	36	19.4	81	20.5	
Widowed	3	2.7	1	1.0	3	1.6	7	1.8	
Unmarried	81	73.6	32	32.3	79	42.5	192	48.6	
Childless patients	97	89.0	58	59.8	130	70.7	285	73.1	<0.001[a]
Secondary/higher education	68	61.8	71	71.7	121	65.1	260	65.8	0.307[a]
Smokers	57	51.8	50	50.5	78	42.2	185	47.0	0.197[a]
Inpatients	36	31.9	20	20.2	34	18.1	90	22.5	0.028[a]
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		*P*-value
Age	44.3 (12.4)		43.4 (12.3)		41.2 (13.3)		42.6 (12.9)		0.112[b]
Age of onset	30.4 (13.1)		34.7 (14.2)		35.2 (14.3)		33.0 (14.2)		0.009[b]
Duration of illness	14.6 (13.8)		9.1 (8.6)		6.3 (4.8)		9.8 (8.7)		0.001[b]

SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder
[a] Chi-square test.
[b] Kruskal–Wallis test.

3.2. Overall Anxiety Severity and Impairment Scale (OASIS)

The mean scores of OASIS (Table 2) from 9.4 to 11.0 were seemingly close to each other, but nevertheless differed significantly ($P = 0.040$). Of specific subgroups, childless SSA and DD patients had higher OASIS scores ($P = 0.001$ and $P = 0.026$, respectively), as did smokers with BD ($P = 0.006$). Analyses demonstrated no significant relations between OASIS scores and other sociodemographic and background variables (data not shown). Overall, from 40.2% to 55.6% of the patients of all groups reported experiencing anxiety frequently or constantly; from 41.2% to 43.8% felt anxiety as severe or extreme (Table 3). SSA patients felt frequent or constant anxiety less often than BD and DD patients ($P = 0.010$) and did not avoid anxiety-provoking situations as often as BD and DD patients ($P = 0.009$). Severe or extreme anxiety interfered with functioning at home, school, and work in 33.9% of SSA, 40.4% of BD, and 40.1% of DD patients (OASIS item 4). The corresponding figures for anxiety-induced impairment in social life and relationships were 35.7%, 33.4%, and 44.3% (OASIS item 5). However, the differences between diagnostic groups in these two last items were not statistically significant.

Table 2
OASIS scores distributions: comparison between diagnostic groups.

	SSA ($n = 113$)	BD ($n = 99$)	DD ($n = 188$)
Mean* (SD)	9.4 (5.5)	10.8 (4.4)	11.0 (4.8)
Percentiles			
10	4.0	4.0	4.0
25	5.0	7.0	8.0
50	10.0	12.0	12.0
75	14.0	14.0	15.0
90	16.0	16.0	17.0

SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder.
* $P = 0.040$ (Kruskal–Wallis test).

Table 3
Results of the OASIS questionnaire items by diagnostic group.

	SSA (n = 113)		BD (n = 99)		DD (n = 188)	
	n	%	n	%	n	%
How often have you felt anxious*						
No anxiety	18	16.1	4	4.0	10	5.3
Infrequent anxiety	21	18.8	15	15.2	29	15.5
Occasional anxiety	28	25.0	29	29.3	44	23.5
Frequent anxiety	32	28.6	41	41.4	76	40.6
Constant anxiety	13	11.6	10	10.1	28	15.0
When you have felt anxious, how intense or severe was your anxiety						
Little or None	16	14.3	3	3.0	7	3.7
Mild	18	16.1	20	20.2	35	18.7
Moderate	29	25.9	35	35.4	68	36.4
Severe	42	37.5	31	31.3	68	36.4
Extreme	7	6.3	10	10.1	9	4.8
How often did you avoid situations, places, objects, or activities because of anxiety or fear**						
None	23	20.4	14	14.1	20	10.6
Infrequent	23	20.4	14	14.1	34	18.1
Occasional	38	33.6	29	29.3	54	28.7
Frequent	20	17.7	32	32.3	65	34.6
All the time	9	8.0	10	10.1	15	8.0
How much did your anxiety interfere with your ability to do the things you needed to do at work, at school, or at home						
None	27	24.1	11	11.1	18	9.6
Mild	17	15.2	21	21.2	36	19.3
Moderate	30	26.8	27	27.3	58	31.0
Severe	26	23.2	32	32.3	52	27.8
Extreme	12	10.7	8	8.1	23	12.3
How much has anxiety interfered with your social life and relationships						
None	22	19.6	8	8.1	16	8.6
Mild	22	19.6	24	24.2	46	24.6
Moderate	28	25.0	34	34.3	44	23.5
Severe	29	25.9	26	26.3	51	27.3
Extreme	11	9.8	7	7.1	30	16.0

SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder.
* P = 0.010.
** P = 0.009 (Kruskal–Wallis test).

3.3. OASIS correlation with other measures

Overall, OASIS correlated mainly with the same scales in all groups (Table 4). The strong correlation between anxiety and depression symptoms was found in each diagnostic group. Noteworthy is that all patients experienced fairly severe depressive symptoms (data not shown). High neuroticism and anxiety correlated strongly in the SSA group and moderately in the BD and DD groups. In all patients, anxiety symptoms had a moderate direct correlation with the symptoms of borderline personality disorder (MSI) and early trauma (TADS), and a weak direct correlation with anxious attachment style (ECR anxiety). Across all the diagnostic groups, patients with more severe anxiety symptoms tended to have a lower self-efficacy level, as there was a moderate inverse correlation between OASIS and GSE. In addition, avoidant attachment style (ECR avoidance) showed a weak direct correlation with anxiety symptoms only in the BD and DD groups.

Table 4
Bivariate correlation between OASIS and other rating scales by diagnostic group (Spearman's rank).

	BDI	S5N	MSI	GSE	TADS	ECR anxiety	ECR avoidance
SSA (n = 113)	.700***	.712***	.588***	−.448***	.498***	.350**	−.017
BD (n = 99)	.729***	.569***	.447***	−.398***	.498***	.365***	.232*
DD (n = 188	.700***	.584***	.457***	−.440***	.413***	.273**	.203*

SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder; OASIS: Overall Anxiety Severity and Impairment Scale; BDI: Beck Depression Inventory; S5N: "Short Five" Neuroticism Scale; MSI: McLean Screening Instrument for Borderline Personality Disorder; GSE: General Self-Efficacy scale; TADS: Trauma and Distress Scale; ECR: Experiences in Close Relationships; ECR anxiety: ECR questionnaire items 1–18; ECR avoidance: ECR questionnaire items 19–36.
* $P \leq 0.05$.
** $P \leq 0.01$.
*** $P \leq 0.001$.

3.4. Regression analysis

Of all the variables, symptoms of depression (BDI) and high neuroticism (S5N) were the most strongly associated with OASIS in different regression models (Table 5). Surprisingly, in the main model with all the variables, neuroticism showed a significant weight in the SSA and DD groups, but not in the BD group. In the same model, depressive symptoms were significantly associated with OASIS in the BD and DD groups. When BDI and S5N were both excluded from the regression model, the symptoms of borderline personality disorder and level of self-efficacy acquired a regression weight in each diagnostic group and the early trauma and distress in the BD and DD groups.

4. Discussion

The current study investigated comorbid anxiety symptoms from both clinical and theoretical viewpoints. The clinical aim was to examine the point prevalence and level of comorbid anxiety symptoms across the major psychiatric disorders in specialized

Table 5
Clinical correlates for OASIS by diagnosis group (linear regression analysis). The main analysis showed in the first model (analysis with all variables).

	SSA (n = 113)		BD (n = 99)		DD (n = 188)	
	B	Sig.	B	Sig.	B	Sig.
Analysis with all variables						
Sex	−.845	.396	−.647	.370	−.595	.415
Age	−.005	.900	.037	.219	.036	.127
BDI	.081	.213	.198	.000	.180	.000
S5N	.148	.007	.086	.053	.094	.007
MSI	.388	.084	.008	.966	.214	.152
GSE	−.007	.934	.072	.330	.007	.913
TADS	.011	.674	.029	.094	.021	.110
ECR anxiety	.024	.214	.002	.879	−.014	.271
Analysis with BDI excluded						
Sex	−.815	.415	−.749	.368	−.499	.540
Age	.001	.981	.053	.126	.037	.159
S5N	.184	.000	.145	.004	.144	.000
MSI	.410	.069	.124	.565	.257	.122
GSE	−.017	.836	.002	.979	−.106	.123
TADS	.019	.456	.050	.011	.043	.003
ECR anxiety	.025	.208	.000	.981	−.020	.170
Analysis with S5N excluded						
Sex	−1.008	.338	−.888	.222	−.368	.620
Age	−.014	.741	.022	.450	.038	.117
BDI	.181	.002	.218	.000	.204	.000
MSI	.585	.011	.169	.331	.382	.007
GSE	−.090	.257	−.001	.982	−.061	.320
TADS	.050	.998	.023	.181	.018	.177
ECR anxiety	.031	.129	.012	.450	−.007	.564
Analysis with BDI and S5N excluded						
Sex	−1.042	.356	−1.202	.163	−.104	.903
Age	−.002	.969	.029	.402	.041	.145
MSI	.812	.001	.436	.030	.544	.001
GSE	−.189	.018	−.144	.045	−.242	.000
TADS	.017	.554	.043	.035	.043	.005
ECR anxiety	.038	.084	.016	.390	−.010	.511

SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder; BDI: Beck Depression Inventory; S5N: "Short Five" Neuroticism Scale; MSI: McLean Screening Instrument for Borderline Personality Disorder; GSE: General Self-Efficacy scale; ECR anxiety: Experiences in Close Relationships questionnaire items 1–18; TADS: Trauma and Distress Scale.

psychiatric care. Overall, almost half of the patients of all diagnostic groups experienced frequently or constantly severe or extreme anxiety. However, anxiety was somewhat less frequent in schizophrenia spectrum disorders (SSA) patients than in their mood disorders counterparts. The theoretical aim was to explore the relationship of anxiety with likely covariates and putative risk factors, and determine whether these are similar across the disorders investigated, which indeed they mostly were.

Strengths of the study include investigation of the similarities and differences in comorbid anxiety symptoms using the same methodology in a relatively large sample (total n 400) of psychiatric patients with different principal diagnoses from the Helsinki metropolitan area psychiatric services. This enabled investigating the covariates and putative risk factors of anxiety symptoms across the major diagnostic groups simultaneously. Anxiety symptoms were measured using the Overall Anxiety Severity and Impairment Scale (OASIS), which have been found to be a valid and reliable brief scale [42]. In addition to frequency and intensity of anxiety symptoms and avoidance due to these symptoms, the OASIS also captures anxiety-related functional and behavioral impairment [51].

Our study had several limitations. First, it was a cross-sectional study, thus not enabling causal inferences regarding risk factors for anxiety symptoms, or any analyses of temporal variations. Second, we used only a self-report measure of anxiety symptoms and did not have interview-based measures of anxiety symptoms. Third, the response rate was only 33%, probably due to sampling conducted during busy routine clinical practice and the length of the survey. However, according to the analysis of representativeness, our sample did not differ from the total patient population regarding age or gender. In terms of other demographic characteristics, our sample corresponded to the large screening-based Vantaa Depression Study and Jorvi Bipolar Study [18,52]. Fourth, the presence, intensity, and quality of current psychotic symptoms were not measured, and thus, their role in comorbidity of anxiety remains unclear. Fifth, retrospective bias may exist in relation to some measurement scales, as patients may not always recollect past events and symptoms. Sixth, the principal clinical diagnoses were not based on structured interviews, although they were validated by the authors based on patients' psychiatric records. Seventh, the study includes multiple statistical analyses, so problems of multiple testing need to be considered. However, there were two hypotheses and one statistical test for each. The remaining analyses are either presented for descriptive purposes, or to confirm coherence and robustness of the hypothesis-related findings irrespective of methodological details.

The clinical aim of the study was to investigate prevalence and patterns of comorbid anxiety symptoms across the disorders. The mean OASIS total scores in all three subgroups clearly exceeded the cut-off score of eight points, usually indicating presence of an AD [42]. Nearly half of our patients in all groups frequently or constantly experienced severe or extreme anxiety. The proportions of our patients with frequent and severe anxiety were similar to findings of lifetime comorbid AD in the same diagnostic groups in earlier reports [6–8]. However, direct comparison of our results with those of previous studies is difficult due to methodological differences and since the published reports rely mostly on categorically diagnosed AD rather than on anxiety symptoms. Of all three subgroups, the SSA patients reported frequent anxiety and anxiety-related avoidance behavior less often than their mood disorder counterparts. The lower rate of comorbid anxiety symptoms in the SSA group could be explained in several ways. First, more frequent anxiety symptoms in patients with mood disorders could be expected because of strong co-incidence of internalizing disorders [21,24–26] as well as temporal covariation of depressive and anxiety symptoms among them [22,53]. However, virtually all of the patients, irrespective of their principal diagnosis, suffered from clinically significant depressive symptoms, which strongly correlated with anxiety symptoms, albeit more in patients with mood disorders than in those with SSA. Second, the majority of SSA patients were outpatients, and thus, in relatively stable condition. For this reason, they probably less often had florid positive symptoms or primary disorder-induced anxiety symptoms to report [9]. Third, avoidance behavior may be less prominent in SSA patients due to their common withdrawal from social roles, and hence, less frequent exposure to common anxiety-provoking situations [54–56]. Furthermore, these patients often experience negative symptoms, rendering some of them emotionally numb and indifferent to situations that tend to cause anxiety in other populations [57]. Nevertheless, despite the observed subgroup differences, we found comorbid anxiety symptoms to be ubiquitous among psychiatric patients with major mood or schizophrenia spectrum disorders, and in almost half of them, reportedly severe. These findings highlight the importance of the recognition and treatment of comorbid anxiety symptoms.

The theoretical focus of our study was in investigating the clinical correlates of comorbid anxiety symptoms and their potential similarities across major psychiatric disorders. We found numerous quite similar associations; in addition to the strongest correlation of the OASIS score with symptoms of depression (BDI) and neuroticism (S5) in all patients, associations emerged also for low self-efficacy (GSE) and symptoms of borderline personality (MSI) across all diagnostic groups, and for early trauma and distress (TADS) in BD and DD patients. In multivariate regression analyses of all clinical variables, neuroticism in SSA patients was associated with comorbid anxiety symptoms as strongly as in DD patients. Therefore, the personality trait of neuroticism seems to be an underlying factor for comorbid anxiety beyond the internalizing domain, thus possibly also within schizophrenia spectrum disorders.

Presence of depressive symptoms and high neuroticism, thus, persisted as independent covariates for anxiety symptoms in multivariate regression models. There were also other correlates associated with anxiety, but not consistently after controlling for the above two factors. These other correlates were mostly the same across the diagnostic groups, with only TADS not being associated with OASIS in the SSA group. Numerous studies suggest an association between experienced childhood trauma and psychotic and mood disorders [31,37,58]. Early traumatic experiences may be connected to a higher level of neuroticism as well [59,60]. Hence, trauma could potentially contribute to comorbid anxiety as a distal cause as well as a neuroticism-mediated condition. In addition, in our patients self-reported symptoms of borderline personality disorder were associated with anxiety symptoms in all diagnostic groups. This finding is consistent with other studies showing that up to 90% of patients with borderline personality disorder experience comorbid anxiety [34,61]. Probably unsurprisingly, also self-efficacy was inversely associated with the level of anxiety and regardless of the primary diagnoses. Poor self-efficacy appears to be a significant factor in development, severity, and treatment of anxiety disorders [32,62]. Our finding suggests that the same logic applies to comorbid anxiety as a continuum. In short, the broad similarity of correlates across all diagnostic groups supports the view that comorbid anxiety symptoms have numerous common background factors, and thus, could be due to a non-aligned condition rather than a direct consequence of the primary psychiatric pathology. While these associations are interesting, it is important to bear in mind their inconsistent significance in multivariate analyses. Analyses of mediation or moderation were beyond the scope of this study. Overall, the most robust and consistent associations with symptoms of anxiety in all subgroups were those with current depressive symptoms and neuroticism.

5. Conclusion

Comorbid anxiety symptoms are highly prevalent among psychiatric patients with major mood or schizophrenia spectrum disorders, and in almost half of them, reportedly severe. The prevalence of symptoms is somewhat higher in the former group than in the latter. In addition, anxiety-related avoidance behavior is less frequent in patients with schizophrenia spectrum disorders. Anxiety symptoms appear strongly related to both concurrent presence of depressive symptoms and personality characteristics, particularly high neuroticism, regardless of the principal diagnosis.

Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Öhman A. Fear and anxiety: overlaps and dissociations. In: Lewis M, Haviland-Jones JM, Barrett LF, editors. Handbook of emotions. New York: The Guilford Press; 2008. p. 709–30.
[2] Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, Severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Arch Gen Psychiatry 2005;62(6):617–27.
[3] Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) Surveys. Epidemiol Psichiatr Soc 2009;18(1):23–33.
[4] Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21(9):655–79.
[5] Pirkola SP, Isometsä ET, Suvisaari J, Aro H, Joukamaa M, Poikolainen K, et al. DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population. Results from the Health 2000 Study. Soc Psychiatry Psychiatr Epidemiol 2005;40(1):1–10.
[6] Achim AM, Maziade M, Raymond E, Olivier D, Merette C, Roy MA. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. Schizophr Bull 2011;37(4):811–21.
[7] Pavlova B, Perlis RH, Alda M, Uher R. Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry 2015;2(8):710–7.
[8] Brown TA, Campbell LA, Lehman CL, Grisham JR, Mancill RB. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol 2001;110(4):585–99.
[9] Braga RJ, Reynolds GP, Siris SG. Anxiety comorbidity in schizophrenia. Psychiatry Res 2013;210(1):1–7.
[10] El-Mallakh RS, Hollifield M. Comorbid anxiety in bipolar disorder alters treatment prognosis. Psychiatr Q 2008;79(2):139–50.
[11] Braam AW, Copeland JR, Delespaul PA, Beekman AT, Como A, Dewey M, et al. Depression, subthreshold depression and comorbid anxiety symptoms in older Europeans: results from the EURODEP concerted action. J Affect Disord 2014;155:266–72.
[12] Saarni SI, Suvisaari J, Sintonen H, Pirkola S, Koskinen S, Aromaa A, et al. Impact of psychiatric disorders on health-related quality of life: general population survey. Br J Psychiatry 2007;190:326–32.
[13] Comer JS, Blanco C, Hasin DS, Liu S-M, Grant BF, Turner JB, et al. Health-related quality of life across the anxiety disorders. J Clin Psychiatry 2011;72(1):43–50.
[14] Karsten J, Penninx BW, Verboom CE, Nolen WA, Hartman CA. Course and risk factors of functional impairment in subthreshold depression and anxiety. Depress Anxiety 2013;30(4):386–94.
[15] Miloyan B, Byrne GJ, Pachana NA. Threshold and subthreshold generalized anxiety disorder in later life. Am J Geriatr Psychiatry 2015;23(6):633–41.
[16] Weiller E, Bisserbe JC, Maier W, Lecrubier Y. Prevalence and recognition of anxiety syndromes in five European primary care settings: a report from the WHO study on psychological problems in general health care. Br J Psychiatry Suppl 1998;34:18–23.
[17] Mantere O, Melartin TK, Suominen K, Rytsala HJ, Valtonen HM, Arvilommi P, et al. Differences in Axis I and II comorbidity between bipolar I and II disorders and major depressive disorder. J Clin Psychiatry 2006;67(4):584–93.
[18] Melartin TK, Rytsala HJ, Leskela US, Lestela-Mielonen PS, Sokero TP, Isometsa ET. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. J Clin Psychiatry 2002;63(2):126–34.
[19] Lysaker PH, Salyers MP. Anxiety symptoms in schizophrenia spectrum disorders: associations with social function, positive and negative symptoms, hope and trauma history. Acta Psychiatr Scand 2007;114(4):290–8.
[20] Krueger RF, Caspi A, Moffitt TE, Silva PA. The structure and stability of common mental disorders (DSM-III-R): a longitudinal-epidemiological study. J. Abnorm Psychol 1998;107(2):216–27.
[21] Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry 1999;56(10):921–6.
[22] Melartin T, Mantere O, Ketokivi M, Isometsä E. A prospective latent analysis study of Axis I psychiatric co-morbidity of DSM-IV major depressive disorder. Psychol Med 2014;44(5):949–59.
[23] Eaton NR, Krueger RF, Markon KE, Keyes KM, Skodol AE, Wall M, et al. The structure and predictive validity of the internalizing disorders. J Abnorm Psychol 2013;122(1):86–92.
[24] Kessler RC, Ormel J, Petukhova M, McLaughlin KA, Green JG, Russo LJ, et al. Development of lifetime comorbidity in the WHO World Mental Health (WMH) Surveys. Arch Gen Psychiatry 2011;68(1):90–100.
[25] Kendler KS, Aggen SH, Knudsen GP, Røysamb E, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. Am J Psychiatry 2011;168(1):29–39.
[26] Hettema JM. What is the genetic relationship between anxiety and depression? Am J Med Genet C 2008;148C(2):140–6.
[27] Mantere O, Soronen P, Uher R, Ketokivi M, Jylha P, Melartin T, et al. Neuroticism mediates the effect of P2RX7 on outcomes of mood disorders. Depress Anxiety 2012;29(9):816–23.
[28] Ormel J, Jeronimus BF, Kotov R, Riese H, Bos EH, Hankin B, et al. Neuroticism and common mental disorders: meaning and utility of a complex relationship. Clin Psychol Rev 2013;33(5):686–97.
[29] Griffith JW, Zinbarg RE, Craske MG, Mineka S, Rose RD, Waters AM, et al. Neuroticism as a common dimension in the internalizing disorders. Psychol Med 2010;40(7):1125–36.
[30] de Moor MH, van den Berg SM, Verweij KJ, Krueger RF, Luciano M, Arias Vasquez A, et al. Meta-analysis of genome-wide association studies for neuroticism, and the polygenic association with major depressive disorder. JAMA Psychiatry 2015;72(7):642–50.
[31] Hovens JG, Giltay EJ, Wiersma JE, Spinhoven P, Penninx BW, Zitman FG. Impact of childhood life events and trauma on the course of depressive and anxiety disorders. Acta Psychiatr Scand 2012;126(3):198–207.
[32] Richards JC, Richardson V, Pier C. The relative contributions of negative cognitions and self-efficacy to severity of panic attacks in panic disorder. Behav Change 2002;19(2):102–11.
[33] De Las Cuevas C, Penate W, Sanz EJ. The relationship of psychological reactance, health locus of control and sense of self-efficacy with adherence to treatment in psychiatric outpatients with depression. BMC Psychiatry 2014; 14:324.
[34] Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, et al. comorbidity of borderline personality disorder. Am J Psychiatry 1998;155(12): 1733–9.
[35] Marazziti D, Dell'osso B, Catena Dell'Osso M, Consoli G, Del Debbio A, Mungai F, et al. Romantic attachment in patients with mood and anxiety disorders. CNS Spectr 2007;12(10):751–6.
[36] Van Os J, Jones PB. Neuroticism as a risk factor for schizophrenia. Psychol Med 2001;31(6):1129–34.
[37] Larsson S, Andreassen OA, Aas M, Røssberg JI, Mork E, Steen NE, et al. High prevalence of childhood trauma in patients with schizophrenia spectrum and affective disorder. Compr Psychiatry 2013;54(2):123–7.
[38] Kurtz MM, Olfson RH, Rose J. Self-efficacy and functional status in schizophrenia: relationship to insight, cognition and negative symptoms. Schizophr Res 2013;145(1–3):69–74.
[39] Bahorik AL, Eack SM. Examining the course and outcome of individuals diagnosed with schizophrenia and comorbid borderline personality disorder. Schizophr Res 2010;124(1–3):29–35.
[40] International classification of disease, 10th ed., Geneva: World Health Organization; 1992.
[41] Norman SB, Cissell SH, Means-Christensen AJ, Stein MB. Development and validation of an Overall Anxiety Severity and Impairment Scale (OASIS). Depress Anxiety 2006;23(4):245–9.
[42] Campbell-Sills L, Norman SB, Craske MG, Sullivan G, Lang AJ, Chavira DA, et al. Validation of a brief measure of anxiety-related severity and impairment: the Overall Anxiety Severity and Impairment Scale (OASIS). J Affect Disord 2009;112(1–3):92–101.
[43] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
[44] Konstabel K, Lönnqvist J-E, Walkowitz G, Konstabel K, Verkasalo M, et al. The 'Short Five' (S5): measuring personality traits using comprehensive single items. Eur J Pers 2012;26(1):13–29.
[45] Fraley RC, Waller NG, Brennan KA. An item response theory analysis of self-report measures of adult attachment. J Pers Soc Psychol 2000;78:350–65.
[46] Schwarzer R, Jerusalem M. Generalized Self-Efficacy scale. In: Weinman J, Wright S, Johnston M, editors. Measures in health psychology: A user's portfolio. Causal and control beliefs. UK: Windsor; 1995. p. 35–7.
[47] Zanarini MC, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J. A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). J Pers Disord 2003;17(6): 568–73.

[48] Patterson P, Skeate A, Schultze-Lutter F, Graf von Reventlow H, Wieneke A, Ruhrmann S, et al. The Trauma and Distress Scale. Birmingham, UK:University of Birmingham; 2002.
[49] Luutonen S, Tikka M, Karlsson H, Salokangas RK. Childhood trauma and distress experiences associate with psychotic symptoms in patients attending primary and psychiatric outpatient care. Results of the RADEP study. Eur Psychiatry 2013;28(3):154–60.
[50] IBM SPSS Statistics for Windows, Version 22.0. Released 2013. Armonk, NY: IBM Corp; 2013.
[51] Norman SB, Campbell-Sills L, Hitchcock CA, Sullivan S, Rochlin A, Wilkins KC, et al. Psychometrics of a brief measure of anxiety to detect severity and impairment: The overall anxiety severity and impairment scale (OASIS). J Psychiatr Res 2011;45(2):262–8.
[52] Mantere O, Suominen K, Leppämäki S, Valtonen H, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). Bipolar Disord 2004;6(5):395–405.
[53] Mantere O, Isometsä E, Ketokivi M, Kiviruusu O, Suominen K, Valtonen HM, et al. A prospective latent analyses study of psychiatric comorbidity of DSM-IV bipolar I and II disorders. Bipolar Disord 2010;12(3):271–84.
[54] Reddy LF, Green MF, Rizzo S, Sugar CA, Blanchard JJ, Gur RE, et al. Behavioral approach and avoidance in schizophrenia: an evaluation of motivational profiles. Schizophr Res 2014;159(1):164–70.
[55] Konstantakopoulos G, Ploumpidis D, Oulis P, Patrikelis P, Soumani A, Papadimitriou GN, et al. Apathy, cognitive deficits and functional impairment in schizophrenia. Schizophr Res 2011;133(1–3):193–8.
[56] Hansen CF, Torgalsboen AK, Rossberg JI, Romm KL, Andreassen OA, Bell MD, et al. Object relations, reality testing, and social withdrawal in schizophrenia and bipolar disorder. J Nerv Ment Dis 2013;201(3):222–5.
[57] Foussias G, Agid O, Fervaha G, Remington G. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. Eur Neuropsychopharmacol 2014;24(5):693–709.
[58] Weber K, Rockstroh B, Borgelt J, Awiszus B, Popov T, Hoffmann K, et al. Stress load during childhood affects psychopathology in psychiatric patients. BMC Psychiatry 2008;8:63.
[59] McFarlane A, Clark CR, Bryant RA, Williams LM, Niaura R, Paul RH, et al. The impact of early life stress on psychophysiological, personality and behavioral measures in 740 non-clinical subjects. J Integr Neurosci 2005;4(1):27–40.
[60] Roy A. Childhood trauma and neuroticism as an adult: possible implication for the development of the common psychiatric disorders and suicidal behavior. Psychol Med 2002;32(8):1471–4.
[61] Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2008;69(4):533–45.
[62] Gallagher MW, Payne LA, White KS, Shear KM, Woods SW, Gorman JM, et al. Mechanisms of change in cognitive behavioral therapy for panic disorder: the unique effects of self-efficacy and anxiety sensitivity. Behav Res Ther 2013;51(11):767–77.

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Psychoactive substance use in specialized psychiatric care patients

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Abstract

Objective: Life expectancy of psychiatric patients is markedly shorter compared to the general population, likely partly due to smoking or misuse of other substances. We investigated prevalence and correlates of substance use among psychiatric patients.

Methods: Within the Helsinki University Psychiatric Consortium Study, data were collected on substance use (alcohol, smoking, and illicit drugs) among patients with schizophrenia or schizoaffective disorder (n = 113), bipolar (n = 99), or depressive disorder (n = 188). Clinical diagnoses of substance use were recorded, and information on smoking, hazardous alcohol use, or misuse of other substances was obtained using questionnaires.

Results: One-fourth (27.7%) of the patients had clinical diagnoses of substance use disorders. In addition, in the Alcohol Use Disorders Identification Test, 43.1% had hazardous alcohol use and 38.4% were daily smokers. All substance use was more

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common in men than in women. Bipolar patients had the highest prevalence of alcohol use disorders and hazardous use, whereas those with schizophrenia or schizoaffective disorder were more often daily smokers. In regression analyses, self-reported alcohol consumption was associated with symptoms of anxiety and borderline personality disorder and low conscientiousness. No associations emerged for smoking.
Conclusions: The vast majority of psychiatric care patients have a diagnosed substance use disorder, hazardous alcohol use, or smoke daily, males more often than females. Bipolar patients have the highest rates of alcohol misuse, schizophrenia or schizoaffective disorder patients of smoking. Alcohol use may associate with symptoms of anxiety, borderline personality disorder, and low conscientiousness. Preventive and treatment efforts specifically targeted at harmful substance use among psychiatric patients are necessary.

Keywords
substance use, alcohol misuse, smoking, psychiatric care

Introduction

Substance use disorders (SUDs) are a serious social and economic issue,[1] with a major adverse impact on public health and welfare worldwide.[2,3] In the general population, the 12-month prevalence of SUDs is estimated at 3.9–13.9% and the lifetime prevalence at 9.9–29.1%.[4–6] Numerous general population and clinical sample studies show that the proportion of SUDs among persons with mental disorders is much higher, reaching 20.0% over a 12-month period and 50.9% over the lifetime.[7–9] Cooccurring SUDs expand the burden of mental disorders by worsening their course and outcome[10,11] and impairing the general quality of life.[12] More importantly, SUD comorbidity is often associated with increased physical morbidity[13,14] and suicidal behavior,[15,16] both resulting in early mortality.[17]

Analogously, smoking is a major public health problem. While mitigated worldwide in the previous decades to 21% in the general population aged 15 years and over,[18] it remains high among psychiatric patients[19] whose 12-month and lifetime estimates for smoking prevalence are 31% and 56%,[20,21] respectively. The prevalences are even higher when mental disorders are accompanied by an SUD.[22] Similar to SUDs, smoking in psychiatric patients is associated with increased premature mortality rates.[23,24]

Despite the high prevalence and well-known detrimental effects of substance use and smoking, they often go unrecognized or unmonitored in psychiatric clinical practice[25,26] and, thus, untreated.[4,27] This may be of considerable importance regarding the curtailed (by 10–20 years) life expectancy of psychiatric patients relative to the general population,[28,29] which is likely affected by mortality attributable to alcohol, tobacco, and illicit drug use.

Overall, SUDs and smoking comprise major research topics themselves, with vast bodies of epidemiological literature available. However, relatively few studies have investigated (1) the prevalence of substance use and smoking, (2) their cooccurrence, and (3) their correlates among psychiatric patients with major psychiatric disorders, and thus, at high risk for acquiring them and their adverse health consequences. Our study aims to obtain such data. First, we expected substance use to be highly prevalent and also, based on findings from general population studies,[4,5] more common in men than in women within our specialized psychiatric care sample. In addition, we hypothesized that of all diagnostic groups, alcohol consumption would be more typical for patients with bipolar disorder (BD)[30] and smoking and nonalcohol substance use for those with schizophrenia spectrum disorders.[10,20] Second, we expected a high substance use and smoking to cooccur beyond chance. Third, based on previous findings,[31–35] we expected symptoms of anxiety and borderline personality, as well as personality traits, and to some extent early trauma to be related to more severe substance use across major mental disorders.

Methods

Setting

As described in more detail elsewhere,[36] the Helsinki University Psychiatric Consortium pilot study was performed in the metropolitan area of Helsinki during 2011–2012. Based on stratified random sampling of patients, it was carried out in 10 community mental health centers, 24 psychiatric inpatient units, 1 day-care hospital, and t2 residential communities.

Sampling

Inclusion criteria were age from 18 to 64 years and provision of written informed consent. Of the 1361 eligible patients, 610 declined to participate and 304 were lost for other reasons. The final number of participants was 447, yielding a response rate of 33%.

Online survey

The online survey included a large set of psychometrically sound self-report questionnaires for evaluation of sociodemographic and clinical characteristics of the patients.[36] Use of self-report enabled collecting wide range of information in a relatively short time.

Diagnostic assessment

Diagnostic assessments were made according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision,[37] following the principle of lifetime main diagnosis. SUD diagnoses were gathered as secondary (comorbid) diagnoses. SUDs were classified as alcohol use disorders (AUDs) and other substance use-related disorders (other SUDs). Our patients did not have nicotine use-related diagnoses, as it is commonly neglected in routine clinical practice. For the current study, patients were divided into three subgroups according to the most common principal diagnoses: schizophrenia (F20.00–F20.9) or schizoaffective disorder (F25.00–F25.9; SSA: n = 113), bipolar disorder (F31.00–F31.9; BD: n = 99), and depressive disorder (F32.00–F33.9, F34.1; DD: n = 188).

Substance use measures

The Alcohol Use Disorders Identification Test (AUDIT)[38] is a self-report questionnaire to assess alcohol consumption, alcohol dependence symptoms, and alcohol-related problems (Hazardous Alcohol Use, Dependence Symptoms, and Harmful Alcohol Use domains). An AUDIT score of $\geq$8 for men and $\geq$7 for women suggests hazardous and harmful alcohol use.

Use of nonalcohol drugs was examined with a self-report screen questionnaire for the Psychiatric Research Interview for Substance and Mental Disorders.[39] The screen questionnaire includes two 10-item scales (substance use six times or over three consecutive days) for preceding 12-month nonalcohol substance abuse.

In addition, using questionnaire from Holma et al.,[31] patients were asked about their smoking behavior and history (with the following options: never smoked, quit smoking, smoke occasionally, and smoke daily) and the number of cigarettes smoked per day.

Other measures

The Overall Anxiety Severity and Impairment Scale (OASIS)[40] is a self-report questionnaire to assess severity and impairment associated with anxiety. The Beck Depression Inventory (BDI)[41] is a self-report questionnaire for measuring the severity of depression symptoms. The "Short Five" (S5)[42] is a questionnaire to assess personal traits of neuroticism (S5 N), extraversion (S5 E), openness (S5 O), agreeableness (S5 A), and conscientiousness (S5 C). The McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD, hereafter MSI)[43] is the self-report questionnaire to screen for borderline personality disorder (BPD). The Trauma and Distress Scale (TADS)[44,45] is a self-report scale for the assessment of childhood and early adulthood traumatic experiences and distress. All of the scales had at least good internal consistency

(Cronbach's alpha for AUDIT 0.90; OASIS 0.84; BDI 0.91; S5 scales 0.85–0.88; MSI 0.92; TADS 0.80).

Statistical analyses

The SUDs- and smoking-related nominal and ordinal variables were analyzed *per se* and recoded into dichotomous variables. Thus, we established groups of patients with or without a diagnosis of AUD and either daily smokers or non-smokers. In addition, the sample was stratified into age intervals of 10 years for more specific analysis on relationships of age patterns of substance use and smoking. Regarding educational level, patients were divided into groups of those with primary and professional (secondary and higher) education.

Patients with AUDIT exceeding gender-specific cut-off score were designated as "AUDIT-positive." To explore substance use by diagnosis, we formed two dichotomous variables of (1) SSA and (2) BD versus other major disorders together. The relationships between nominal variables were explored with the chi-square test and between continuous variables with the Spearman's correlation analysis. The Mann–Whitney U test was used to estimate the distribution of continuous variables across dichotomous variables and the Kruskal–Wallis test across nominal/ordinal variables. Linear regression analysis was used to investigate relationships between AUDIT, smoking status, and clinical measurements. In addition, regression model was adjusted for principal diagnoses (SSA, BD, and DD) formed as three nominal variables (yes/no). Interaction analyses were performed to investigate the effect of principal diagnoses on the background factors of alcohol use. Possible contribution of different variables to smoking status was explored with a logistic regression model. Statistical analysis was performed using the Statistical Package for the Social Sciences.[46]

Results

Sociodemographic and background data

The patients were middle aged, with significant between-group differences in age (Table 1). The majority of the patients were females, with the exception of the SSA group, where sex distribution was nearly equal. The SSA patients were significantly more often unmarried and childless than those in the BD and DD groups. The majority of the patients had at least secondary education. The proportion of inpatients was highest in the SSA group, followed by the BD and DD groups ($p = 0.018$).

More than one-third of the patients were daily smokers, with the highest proportion in the SSA group; however, differences were not statistically significant. Among patients with a diagnosis of SUD (27.7%), those having AUDs predominated. Men had SUD and AUD diagnoses more often than women

Table 1. Sociodemographic and clinical characteristics of the sample.

	Total		SSA		BD		DD		p value
	n	%	n	%	n	%	n	%	
Number	447	100.0	113	25.3	99	22.1	188	42.1	
Female	294	65.8	54	47.8	63	63.6	146	77.7	<0.001[a]
Marital status									<0.001[a]
Married/cohabitating	127	28.8	10	9.1	37	37.4	68	36.6	
Divorced/widowed	94	21.3	19	17.3	30	30.3	39	21.0	
Unmarried	220	49.9	81	73.6	32	32.3	79	42.4	
No children	322	72.0	97	89.0	58	59.8	130	70.7	<0.001[a]
Professional education	286	64.0	68	61.8	71	71.7	121	65.1	0.273[a]
Daily smoking	169	37.8	49	43.4	39	39.4	64	34.0	0.387[a]
SUD diagnosis	124	27.7	35	31.0	38	38.4	36	19.1	0.004[a]
Male[b]		39.9[c]		39.0		44.4		31.0	
Female[d]		21.4		22.2		35.0		15.7	
AUD diagnosis	96	21.5	25	22.1	30	30.3	29	15.4	0.027[a]
Male[b]		30.1[c]		25.9		38.9		23.8	
Female[d]		17.0		18.5		25.4		13.1	
Other SUD diagnosis									
Cannabis	7	1.7	5	4.4	—	—	1	0.5	
Sedative or anxiolytic	7	1.7	—	—	4	4.0	2	1.0	
Other stimulant	2	0.4	1	0.9	1	1.0	—	—	
Inhalant	1	0.2	1	0.9	—	—	—	—	
Other psychoactive	11	2.5	3	2.7	3	3.0	4	2.1	
Inpatients	102	22.8	36	31.9	20	20.2	34	18.1	0.018[a]
Age, mean (SD), y	42.0 (13.0)		44.3 (12.4)		43.4 (12.3)		41.2 (13.3)		0.002[e]

Note. AUD = alcohol use disorder; BD = bipolar disorder; DD = depressive disorder; SSA = schizophrenia or schizoaffective disorder; SUD = substance use disorder (including AUD).
[a]Chi-square test.
[b]Of all male patients.
[c]$p < 0.001$, chi-square test (within-group comparison).
[d]Of all female patients.
[e]Kruskal–Wallis test (between-group comparison).

($p = 0.001$). Of the diagnostic subgroups, the BD group had significantly more patients with SUD and AUD.

Prevalence of hazardous alcohol use and AUDs

Almost half of the patients reported at least hazardous alcohol use (Table 2). The AUDIT mean score was higher in men than in women ($p < 0.001$). AUDIT score had a weak inverse correlation with age ($r = -0.150$, $p = 0.023$). However, differences in distributions of AUDIT scores across age intervals were not

Table 2. AUDIT-measured alcohol use.

	Total (n = 447)		SSA (n = 113)		BD (n = 99)		DD (n = 188)		p value
AUDIT scores, mean (SD)									
All	7.5 (7.8)		6.8 (7.3)		8.7 (7.5)		6.7 (7.4)		0.027[a]
Male	9.5 (8.3)**		8.4 (7.7)*		11.1 (7.0)*		9.1 (8.4)*		
Female	6.6 (7.4)		5.0 (6.4)		7.4 (7.5)		5.9 (6.9)		
AUDIT-positive patients	n	%	n	%	n	%	n	%	
All	193	43.1	44	38.9	53	53.5	71	37.8	
Male[b]	82	53.9	29	50.0	25	69.4	20	47.6	0.202[c]
Female[d]	111	37.8	15	27.8	28	44.4	51	35.2	0.052[c]
AUDIT-positive patients									
Without AUD diagnosis									
Male	46	56.1	17	58.6	13	52.0	12	60.0	0.836[c]
Female	72	64.9	9	60.0	16	57.1	34	66.6	0.684[c]
AUDIT scores, mean (SD)									
Patients with AUD									
Male	17.7 (7.5)		17.3 (7.3)		15.3 (4.6)		17.1 (7.1)		
Female	18.4 (8.9)		16.3 (5.9)		16.1 (7.9)		17.5 (8.4)		
Patients without AUD									
Male	13.7 (5.5)		12.8 (3.6)		14.6 (4.5)		14.4 (8.6)		
Female	11.6 (4.3)		12.7 (4.1)		12.5 (4.8)		11.3 (4.5)		

Note. AUDIT = Alcohol Use Disorders Identification Test; AUDIT-positive = AUDIT score $\geq$ 8 for men and $\geq$ 7 for women; AUD = alcohol use disorder; SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder.

[a]Kruskal–Wallis test (between-group comparison).

[b]Of all male patients.

[c]Chi-square test.

[d]Of all female patients.

*$p < 0.05$, **$p < 0.001$, chi-square test (within-group comparison).

significant, and no associations emerged for any other sociodemographic factors (data not shown). The BD group had significantly higher AUDIT scores than the SSA and DD groups ($p = 0.007$). Mean AUDIT score exceeded the cut-off level for harmful alcohol use in men in the total sample and in all diagnostic groups, and in women in the BD group.

Overall, 43.1% of the total sample patients were found to be AUDIT-positive. In AUDIT-positive male patients, the mean AUDIT score was 15.4 (SD 6.7), and in female patients 14.0 (SD 7.1), thus clearly exceeding gender-specific cut-off scores and suggesting high-risk alcohol use. Nevertheless, of all AUDIT-positive patients, only 38.9% had an AUD diagnosis ($p < 0.001$). Those without diagnoses had, however, a mean AUDIT score of 13.7 for men and 11.6 for women (Table 2), more than half (7.4 and 6.7, respectively) of which originated from the domains of dependence symptoms and harmful alcohol use.

Table 3. Smoking status and characteristics of daily smoking.

	Total		SSA		BD		DD		p value
	n	%	n	%	n	%	n	%	
Never smoked	136	30.8	28	25.5	27	27.3	63	34.1	0.443[a]
Quit smoking	97	22.0	25	22.7	22	22.2	44	23.8	
Occasional smoking	39	8.8	8	7.3	11	11.1	14	7.6	
Daily smoking	169	38.4	49	44.5	39	39.4	64	34.6	
Male[b]		40.3		50.0		36.1		36.6	
Female[c]		37.3		38.9		41.3		34.0	
Smokers with AUD	55	32.5	15	30.6	16	41.0	18	28.1	0.575[a]
Smokers with other SUD	13	7.7	6	12.2	3	7.7	2	3.1	
Daily smokers									
Cigarettes per day, mean (SD)	16.4 (7.7)		18.9 (8.7)		16.2 (7.2)		15.0 (7.2)		0.334[d]
AUDIT scores, mean (SD)	9.8 (8.7)		8.1 (7.2)		10.8 (7.8)		9.6 (8.5)		0.329[d]

AUD = alcohol use disorder; AUDIT = Alcohol Use Disorders Identification Test; BD = bipolar disorder; DD = depressive disorder; SSA = schizophrenia or schizoaffective disorder; SUD = substance use disorder.

[a]Chi-square test.

[b]Of all male patients.

[c]Of all female patients.

[d]Kruskal–Wallis test (between-group comparison).

Smoking

Only one-third of the patients had no history of smoking. Current daily smoking was reported by 38.4%, with no significant gender differences (Table 3). With exception of over 65-year-old patients, who smoked less than the other patients, smoking distribution was balanced across the age groups, with no statistically significant differences (data not shown). Daily smoking emerged significantly more often in patients with primary education than in those with higher education ($p = 0.001$). No other sociodemographic factor was associated with smoking or number of cigarettes smoked per day. Subjects with SSA were more often daily smokers, with the highest number of cigarettes smoked per day, compared with affective disorder patients. This distinction was not, however, statistically significant ($p = 0.128$ and $p = 0.105$, respectively).

Nonalcohol substances

Only 6.5% of the patients had been assigned clinical diagnoses of other SUDs (Table 1). Self-reported use of cocaine, heroin, hallucinogens, stimulants, and opioids (as prescription pain medications) in the total sample was also fairly low, varying from 0.4% (heroin) to 2.7% (opioids). Cannabis consumption of at

least six times within the last 12 months was reported by 5.6% of patients, with 2.7% using cannabis over at least three consecutive days.

Associations between alcohol, nicotine, and nonalcohol substance use

Use of different substances was only weakly intercorrelated. The mean AUDIT score was higher in daily smokers than in nonsmokers ($p < 0.001$), but the number of cigarettes per day did not correlate with AUDIT; only daily smokers with AUD smoked more cigarettes per day than their non-AUD counterparts ($p < 0.001$; data not shown). No other associations emerged between alcohol or nicotine use and nonalcohol substance consumption. Overall, 32.6% of patients neither smoked daily nor had SUD diagnoses, AUDIT-measured hazardous or harmful alcohol use, or any 12-month history of using illicit drugs.

Associations between alcohol use, smoking, and other factors

In linear regression analysis (Table 4), AUDIT score was associated with symptoms of anxiety and borderline personality and with low conscientiousness. Adjustment for principal clinical diagnosis showed that SSA was associated with lower alcohol consumption than BD and DD. Interaction analyses did not reveal any differences in AUDIT distributions within diagnostic groups. Smoking behavior did not interrelate with any analyzed measurement scales in the logistic regression model (data not shown).

Discussion

The current study investigated prevalence, interrelationships, and correlates for substance use within a regionally representative sample of psychiatric patients. About two-thirds of the patients had some form of potentially harmful substance use. Nearly one-third of our patients had a clinical SUD diagnosis. Prevalences of SUD diagnoses and self-reported alcohol misuse were greater in men than in women and in bipolar patients than in other major mental disorders. The SSA group had a higher proportion of patients with nonalcohol drug use and smoking than their affective disorder counterparts. More than one-third of patients smoked daily, which was associated with more intensive alcohol use. Hazardous alcohol use, but not smoking, was associated with symptoms of anxiety and borderline personality, and low conscientiousness.

Prevalence of substance use

The proportion of SUD patients in our study is consistent with previous literature, reporting 19.5–25.0% current comorbidity of mental disorders and SUD in clinical samples.[9,47,48]

Table 4. Bivariate correlation between AUDIT and other rating scales (Spearman's rank).

Basic analysis	Unstandardized coefficient (B)	Sig.
Sex	**−.572**	**.000**
Daily smoking	**.753**	**.000**
Cigarettes per day	.013	.216
OASIS	**.050**	**.007**
MSI	**.063**	**.035**
S5 N	.001	.857
S5 C	**−.020**	**.004**
BDI	.013	.086
TADS	.007	.136
Analyses adjusted for principal diagnoses as dichotomous variables		
Sex	**−.625**	**.000**
Daily smoking	**.750**	**.000**
Cigarettes per day	.011	.306
OASIS	**.047**	**.011**
MSI	**.063**	**.036**
S5 N	.001	.868
S5 C	**−.018**	**.008**
BDI	.013	.103
TADS	.005	.252
SSA	**−.505**	**.027**
BD	−.020	.930
DD	−.255	.243

AUDIT = Alcohol Use Disorders Identification Test; BD = bipolar disorder; BDI = Beck Depression Inventory; DD = depressive disorder; MSI = McLean Screening Instrument for Borderline Personality Disorder; OASIS = Overall Anxiety Severity and Impairment Scale; S5 C = "Short Five" Conscientiousness Scale; S5 N = "Short Five" Neuroticism Scale; SSA = schizophrenia or schizoaffective disorder; TADS = Trauma and Distress Scale.
Statistically significant coefficients are bolded.

The study of Nesvåg et al.[10] is one of the few psychiatric care studies to compare SUDs between major psychiatric disorders. They found that among patients with SSA, BD, and DD, substance use is greatest in the first group. In contrast, our results showed that SUDs and self-reported hazardous or harmful alcohol use emerge more often in BD group. This corresponds to a vast body of literature demonstrating that within major mental disorders, BD patients, especially type I,[49] both in general and in clinical populations have the highest prevalence of SUD (exceeding 60%).[30,50,51] Although some authors[52,53] have

reported up to 60% prevalence of SUD also in schizophrenia spectrum disorders in clinical samples, our results are closer to those of more recent studies,[10,54] with 20–25% of comorbidity rate.

The rate of daily smoking (~40%) in our specialized care study is in accord with the prevalence range (30–67%) for the general population in other countries.[19,20,55] However, our results demonstrate that prevalence of smoking among psychiatric patients remains twofold compared to the general population in Finland.[56] Such figure emphasizes insufficient smoking cessation efforts,[20] despite the availability of treatment methods.[57] Only 30% of our patients had no history of smoking, highlighting widespread nicotine use in psychiatric care, with tremendous somatic health consequences and effect on the metabolism of psychiatric medication.[58]

The distribution of specific substance use across our diagnostic groups was similar to that of previous studies for both general and clinical populations. Thus, in line with reports of Grant et al.[30] and McElroy et al.,[50] our BD patients demonstrated the largest amount of alcohol consumption of all diagnostic groups. In contrast, smoking was more common in our SSA group, consistent with earlier reports showing the highest (up to 70%) smoking prevalence in schizophrenia patients among the major psychiatric disorders.[20,55,59,60] Moreover, analogous to the literature,[10,48] our SSA patients tended to consume nonalcohol drugs more often (28.6% of other SUD diagnoses) than their bipolar and depressive counterparts (21.0% and 19.5%, respectively).

More than a half of our AUDIT-positive patients of both genders did not have any clinical diagnosis of AUD. Nevertheless, as such patients showed high scores in all three AUDIT domains; we assume that the true prevalence of AUDs among AUDIT-positive patients was probably higher. Besides likely underreporting by patients,[61] our finding could reflect the relatively common phenomenon of underestimation of substance abuse by clinicians.[25] Such a phenomenon may result from different factors: First, a general stigmatization of substance use, which holds also for health-care professionals.[62,63] Second, insufficient systematic screening of substance use[64] despite the availability of self-report tests.[65] Third, occasional missing of the relevant substance use-related data in patients' medical records,[66] hindering retrospective SUD diagnosis. In some cases, however, discrepancies between AUD diagnoses and self-reported harmful alcohol use could result from patients' overestimating of drinking behavior.[67] As a result, less than 30% of SUD patients receive proper treatment.[4,5]

Hazardous use of alcohol and daily smoking

The proportions of AUD diagnoses and self-reported alcohol use in daily smokers were higher than in their nonsmoking counterparts. Such cooccurrence is

well known, as many authors have demonstrated that heavy smoking accompanies substance use and dual diagnoses.[20,31,68]

In our sample, alcohol hazardous use was associated with more severe symptoms of anxiety and borderline personality as well as low conscientiousness. A strong cooccurrence of AUDs and anxiety is a well-established finding.[7,69] On the other hand, hazardous use of alcohol in our sample, surprisingly, was not linked to high neuroticism, which is the only S5 personality trait related to the highest comorbidity rates of both internalizing (e.g., anxiety) and externalizing (e.g., substance use) disorders.[32,70] Also, personality trait of conscientiousness, was associated with lower prevalence of hazardous alcohol use, reflecting a likely protective effect of this trait.[71] According to our hypothesis, patients with hazardous alcohol use did have more severe symptoms of borderline personality. Numerous studies have demonstrated such comorbidity, reporting prevalence rates near 80% in patients with diagnosed BPD.[4,72,73]

Overall, substance misuse and smoking were common and interrelated, highlighting the clustering of hazardous lifestyles. Such high-risk patients should be carefully identified both in primary care and in specialized care. Moreover, there is a need for large-scale targeted preventive and treatment efforts focusing on various types and stages of harmful substance use among psychiatric patients.

Strengths and limitations of the study

This study had several strengths. We investigated substance use in a relatively large (n = 447) sample of specialized psychiatric care patients. Information on substance use was collected from both medical records as related diagnoses and patients' self-reports. The study includes a broad spectrum of self-report scales, enabling simultaneous exploration of various associations of substance use across major mental disorders.

Our study also had some limitations. First, it was conducted within a busy clinical practice and included a long survey, which resulted in a relatively low response rate (33%). Nonetheless, register-based analysis of representativeness showed no difference from the patient populations of participating organizations by age or gender. Other demographic characteristics were consistent with the large screening-based studies of the same region.[10,47] Second, this study was cross-sectional, so we were unable to establish any causal or temporal connections between principal disorders and SUDs. Third, results of self-report measures could be affected by retrospective bias or underreporting, especially in relation to illicit substance use. Fourth, neither principal clinical diagnoses nor substance use-related diagnoses were based on structured interviews but were nevertheless verified by the authors by re-examining all available medical records. Fifth, the study included no substance use-related laboratory tests.

Sixth, as the study was performed in the Helsinki metropolitan area, generalizability of the findings to other settings needs to be verified.

Declaration of Conflicting Interests

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References

1. Bouchery EE, Harwood HJ, Sacks JJ, et al. Economic costs of excessive alcohol consumption in the U.S., 2006. *Am J Prev Med* 2011; 41: 516–524.
2. Kessler RC, Aguilar-Gaxiola S, Alonso J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiol Psichiatr Soc* 2009; 18: 23–33.
3. Grant BF, Goldstein RB, Chou SP, et al. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *Mol Psychiatry* 2009; 14: 1051–1066.
4. Grant BF, Goldstein RB, Saha TD, et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry* 2015; 72: 757–766.
5. Grant BF, Saha TD, Ruan WJ, et al. Epidemiology of DSM-5 drug use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry* 2016; 73: 39–47.
6. Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; 21: 655–679.
7. Lai HM, Cleary M, Sitharthan T, et al. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: a systematic review and meta-analysis. *Drug Alcohol Depend* 2015; 154: 1–13.
8. Weaver T, Madden P, Charles V, et al. Comorbidity of substance misuse and mental illness in community mental health and substance misuse services. *Br J Psychiatry* 2003; 183: 304–313.
9. Melartin TK, Rytsälä HJ, Leskelä US, et al. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. *J Clin Psychiatry* 2002; 63: 126–134.
10. Nesvåg R, Knudsen GP, Bakken IJ, et al. Substance use disorders in schizophrenia, bipolar disorder, and depressive illness: a registry-based study. *Soc Psychiatry Psychiatr Epidemiol* 2015; 50: 1267–1276.

11. Margolese HC, Malchy L, Negrete JC, et al. Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences. *Schizophr Res* 2004; 67: 157–166.
12. Whiteford HA, Ferrari AJ, Degenhardt L, et al. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. *PLoS One* 2015; 10: e0116820.
13. Frasch K, Larsen JI, Cordes J, et al. Physical illness in psychiatric inpatients: comparison of patients with and without substance use disorders. *Int J Soc Psychiatry* 2013; 59: 757–764.
14. Dickey B, Normand SL, Weiss RD, et al. Medical morbidity, mental illness, and substance use disorders. *Psychiatr Serv* 2002; 53: 861–867.
15. Schaffer A, Isometsä ET, Tondo L, et al. International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. *Bipolar Disord* 2015; 17: 1–16.
16. Yuodelis-Flores C and Ries RK. Addiction and suicide: a review. *Am J Addict* 2015; 24: 98–104.
17. Hjorthøj C, Østergaard ML, Benros ME, et al. Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study. *Lancet Psychiatry* 2015; 2: 801–808.
18. WHO. WHO global report on trends in tobacco smoking 2000–2025. Geneva: Author, 2015.
19. Grant BF, Hasin DS, Chou SP, et al. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry* 2004; 61: 1107–1115.
20. Smith PH, Mazure CM and McKee SA. Smoking and mental illness in the US population. *Tob Control* 2014; 23: e147–e153.
21. Glasheen C, Hedden SL, Forman-Hoffman VL, et al. Cigarette smoking behaviors among adults with serious mental illness in a nationally representative sample. *Ann Epidemiol* 2014; 24: 776–780.
22. Ferron JC, Brunette MF, He X, et al. Course of smoking and quit attempts among clients with co-occurring severe mental illness and substance use disorders. *Psychiatr Serv* 2011; 62: 353–359.
23. Kelly DL, McMahon RP, Wehring HJ, et al. Cigarette smoking and mortality risk in people with schizophrenia. *Schizophr Bull* 2011; 37: 832–838.
24. Weinberger AH, Mazure CM, Morlett A, et al. Two decades of smoking cessation treatment research on smokers with depression: 1990-2010. *Nicotine Tob Res* 2013; 15: 1014–1031.
25. Oiesvold T, Nivison M, Hansen V, et al. Diagnosing comorbidity in psychiatric hospital: challenging the validity of administrative registers. *BMC Psychiatry* 2013; 13: 13.
26. Williams JM and Ziedonis D. Addressing tobacco among individuals with a mental illness or an addiction. *Addict Behav* 2004; 29: 1067–1083.
27. Shu C and Cook BL. Examining the association between substance use disorder treatment and smoking cessation. *Addiction* 2015; 110: 1015–1024.

28. Walker ER, McGee RE and Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry* 2015; 72: 334–341.
29. Wahlbeck K, Westman J, Nordentoft M, et al. Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. *Br J Psychiatry* 2011; 199: 453–458.
30. Grant BF, Stinson FS, Hasin DS, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2005; 66: 1205–1215.
31. Holma IA, Holma KM, Melartin TK, et al. Depression and smoking: a 5-year prospective study of patients with major depressive disorder. *Depress Anxiety* 2013; 30: 580–588.
32. Khan AA, Jacobson KC, Gardner CO, et al. Personality and comorbidity of common psychiatric disorders. *Br J Psychiatry* 2005; 186: 190–196.
33. Few LR, Grant JD, Trull TJ, et al. Genetic variation in personality traits explains genetic overlap between borderline personality features and substance use disorders. *Addiction* 2014; 109: 2118–2127.
34. Kristjansson S, McCutcheon VV, Agrawal A, et al. The variance shared across forms of childhood trauma is strongly associated with liability for psychiatric and substance use disorders. *Brain Behav* 2016; 6: e00432.
35. Zvolensky MJ, Taha F, Bono A, et al. Big five personality factors and cigarette smoking: a 10-year study among US adults. *J Psychiatr Res* 2015; 63: 91–96.
36. Aaltonen K, Näätänen P, Heikkinen M, et al. Differences and similarities of risk factors for suicidal ideation and attempts among patients with depressive or bipolar disorders. *J Affect Disord* 2016; 193: 318–330.
37. World Health Organization. *International classification of disease*. 10th ed. Geneva: Author, 1992.
38. Babor TF, Saunders J and Grant M. *AUDIT: the alcohol use disorder identification test: guidelines for use in primary health care*. Geneva, Switzerland: Author, 1992.
39. Hasin D, Trautman K, Miele G, et al. Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *AJP* 1996; 153: 1195–1201.
40. Norman SB, Cissell SH, Means-Christensen AJ, et al. Development and validation of an Overall Anxiety Severity and Impairment Scale (OASIS). *Depress Anxiety* 2006; 23: 245–249.
41. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561–571.
42. Konstabel K, Lönnqvist J-E, Walkowitz G, et al. The 'Short Five' (S5): measuring personality traits using comprehensive single items. *Eur J Pers* 2012; 26: 13–29.
43. Zanarini MC, Vujanovic AA, Parachini EA, et al. A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). *J Pers Disord* 2003; 17: 568–573.
44. Patterson P, Skeate A and Birchwood M (ed). *TADS-EPOS 1.2*. Birmingham: University of Birmingham, 2002.

45. Salokangas RK, Schultze-Lutter F, Patterson P, et al. Psychometric properties of the Trauma and Distress Scale, TADS, in an adult community sample in Finland. *Eur J Psychotraumatol* 2016; 7: 30062.
46. IBM. IBM SPSS Statistics for Windows, Version 22.0. Released 2013. Armonk, NY: IBM Corp.
47. Mantere O, Suominen K, Leppämäki S, et al. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). *Bipolar Disord* 2004; 6: 395–405.
48. Ringen PA, Lagerberg TV, Birkenaes AB, et al. Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. *Psychol Med* 2008; 38: 1241–1249.
49. Cerullo MA and Strakowski SM. The prevalence and significance of substance use disorders in bipolar type I and II disorder. *Subst Abuse Treat Prev Policy* 2007; 2: 29.
50. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *AJP* 2001; 158: 420–426.
51. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990; 264: 2511–2518.
52. Fowler IL, Carr VJ, Carter NT, et al. Patterns of current and lifetime substance use in schizophrenia. *Schizophr Bull* 1998; 24: 443–455.
53. Margolese HC, Malchy L, Negrete JC, et al. Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences. *Schizophr Res* 2004; 67: 157–166.
54. Koskinen J, Löhönen J, Koponen H, et al. Prevalence of alcohol use disorders in schizophrenia—a systematic review and meta-analysis. *Acta Psychiatr Scand* 2009; 120: 85–96.
55. Lawrence D, Mitrou F and Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. *BMC Public Health* 2009; 9: 285.
56. Borodulin K, Vartiainen E, Peltonen M, et al. Forty-year trends in cardiovascular risk factors in Finland. *Eur J Public Health* 2015; 25: 539–546.
57. Tidey JW and Miller ME. Smoking cessation and reduction in people with chronic mental illness. *BMJ* 2015; 351: h4065.
58. Desai HD, Seabolt J and Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS Drugs* 2001; 15: 469–494.
59. Jackson JG, Diaz FJ, Lopez L, et al. A combined analysis of worldwide studies demonstrates an association between bipolar disorder and tobacco smoking behaviors in adults. *Bipolar Disord* 2015; 17: 575–597.
60. Dickerson F, Stallings CR, Origoni AE, et al. Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999-2011. *Psychiatr Serv* 2013; 64: 44–50.
61. Devaux M and Sassi F. Social disparities in hazardous alcohol use: self-report bias may lead to incorrect estimates. *Eur J Public Health* 2016; 26: 129–134.
62. Keyes KM, Hatzenbuehler ML, McLaughlin KA, et al. Stigma and treatment for alcohol disorders in the United States. *Am J Epidemiol* 2010; 172: 1364–1372.

63. Crisp AH, Gelder MG, Rix S, et al. Stigmatisation of people with mental illnesses. *Br J Psychiatry* 2000; 177: 4–7.
64. Yoast RA, Wilford BB and Hayashi SW. Encouraging physicians to screen for and intervene in substance use disorders: obstacles and strategies for change. *J Addict Dis*. 2008; 27: 77–97.
65. Babor TF and Kadden RM. Screening and interventions for alcohol and drug problems in medical settings: what works? *J Trauma* 2005; 59: S80–S87; discussion S94–S100.
66. Miller PR. Inpatient diagnostic assessments: 3. Causes and effects of diagnostic imprecision. *Psychiatry Res* 2002; 111: 191–197.
67. Baggio S, Iglesias K, Studer J, et al. Is the relationship between major depressive disorder and self-reported alcohol use disorder an artificial one? *Alcohol* 2015; 50: 195–199.
68. Poirier MF, Canceil O, Baylé F, et al. Prevalence of smoking in psychiatric patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26: 529–537.
69. Kushner MG, Abrams K and Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. *Clin Psychol Rev* 2000; 20: 149–171.
70. Krueger RF and Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. *Annu Rev Clin Psychol* 2006; 2: 111–133.
71. Donadon MF and Osório FL. Personality traits and psychiatric comorbidities in alcohol dependence. *Braz J Med Biol Res* 2016; 49: e5036
72. Trull TJ, Jahng S, Tomko RL, et al. Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substance dependence disorders. *J Pers Disord* 2010; 24: 412–426.
73. Tomko RL, Trull TJ, Wood PK, et al. Characteristics of borderline personality disorder in a community sample: comorbidity, treatment utilization, and general functioning. *J Pers Disord* 2014; 28: 734–750.

III

Self-reported treatment adherence among psychiatric in- and outpatients

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Abstract

Objective: Poor adherence to psychiatric treatment is a common clinical problem, leading to unfavourable treatment outcome and increased healthcare costs. We investigated self-reported adherence and attitudes to outpatient visits and pharmacotherapy in specialized care psychiatric patients.

Methods: Within the Helsinki University Psychiatric Consortium pilot study, in- and outpatients with schizophrenia or schizoaffective disorder (SSA, n=113), bipolar disorder (BD, n=99), or depressive disorder (DD, n=188) were surveyed about their adherence and attitudes towards outpatient visits and pharmacotherapy. Correlates of self-reported adherence to outpatient and drug treatment were investigated using regression analysis.

Results: The majority (78.5%) of patients reported having attended outpatient visits regularly or partly irregularly. Most patients (79.2%) also reported regular use of pharmacotherapy. However, self-reported non-adherence to preceding outpatient visits was consistently and significantly more common among inpatients than outpatients across all diagnostic groups ($p<0.001$). Across all diagnostic groups, hospital setting was the strongest independent correlate of poor adherence to outpatient visits (SSA OR=11.226, BD OR=30.479, DD OR=15.889; $p<0.001$ in all). Another independent correlate of non-adherence was substance use disorder (SSA OR=4.733, $p=0.001$; BD OR=4.643, $p=0.006$; DD OR=9.560, $p<0.000$). No other socio-demographic or clinical factor was significantly associated with poor adherence in multivariate regression models.

Conclusions: Irrespective of diagnosis, self-reported adherence to outpatient care among patients with schizophrenia or schizoaffective disorder, bipolar disorder, and depression is associated strongly with two factors: hospital setting and substance use disorders. Thus, detection of adherence problems among former inpatients and recognition and treatment of substance abuse are important to ensure proper outpatient care.

Index words*: treatment adherence, inpatients, outpatients, psychiatric care.*

Introduction

Adherence to treatment (AT) is a necessary precondition for any treatment to be effective. AT is affected by a spectrum of patient- and disease-related factors, communication, and clinician-patient alliance as well as healthcare system-related factors [1-3]. Treatment non-adherence is a common clinical problem across medical and psychiatric specialties [4,5]. Poor AT in mental disorder patients has a substantial impact on unfavourable treatment outcomes such as lack of remission, increased risk of relapse, and suicidal behaviour [6-9]. Furthermore, disrupted psychiatric treatment contributes to increased healthcare costs and to the global burden of mental disorders [10,11].

The literature on adherence to psychiatric treatment is extensive, although it varies widely by methodology, the population investigated, and definitions of "adherence" in different studies. Adherence is generally understood as correspondence of a patient´s behavior with recommendations of a healthcare professional [4,12,13]. Although this definition encompasses a large spectrum of health-related behaviors, most studies focus on psychopharmacological adherence [14,15]. Thus, other domains of AT, such as adherence to psychosocial treatments or treatment appointments and attitude towards other aspects of treatment, remain poorly investigated.

Because of methodological and conceptual heterogeneity of AT studies, it is hardly surprising that findings on risk factors of non-adherence are largely inconsistent. Most authors concur on substance use comorbidity, negative attitudes to treatment, and poor treatment alliance as well as severe course of illness being common contributors of medication non-adherence across major mental disorders (schizophrenia spectrum, bipolar, and depressive disorders) [16-20].

Data on adherence to psychosocial treatment and outpatient visits are, however, more scarce and diverse. Some studies demonstrate the impact of axis I and II disorders, substance use disorders, affective symptoms, and severe course of illness on non-adherence in bipolar and depressive disorders [17,21,22]. In contrast, adherence to outpatient visits in schizophrenia spectrum disorders has rarely been an object of interest for research, with studies instead investigating interventions aimed at enhancing medication adherence [23]. However, substance abuse in outpatients with schizophrenia is associated with poor attendance of outpatient visits [24].

As the majority of studies on adherence to psychopharmacological and psychosocial treatment comprise one (or rarely two) mental disorder, it remains unclear whether the factors related to non-adherence across a spectrum of psychotic and mood disorders are illness-specific or similar. Furthermore, studies investigating adherence among psychiatric inpatients are scarce. Thus, possible differences in AT between out- and inpatients are not well known.

The current study aimed to investigate AT in patients with major mental disorders (schizophrenia or schizoaffective disorder, bipolar disorder, and depression). Specifically, we examined differences and similarities in prevalence and associations for poor adherence. Based on previous findings and clinical

experience, we hypothesized substance use to be a major contributor to non-adherence irrespective of diagnosis. Furthermore, we expected weaker AT in inpatients than in outpatients.

Methods

The Helsinki University Psychiatric Consortium (HUPC) study has been described in detail in previous publications [25,26] and is summarized below.

Setting

The HUPC study was performed during 2011 – 2012 in secondary mental health services of Helsinki metropolitan area and included 10 community mental health centres, 24 psychiatric inpatient units, one day-care hospital, and two supported housing units. The Ethics Committee of Helsinki University Central Hospital approved the study protocol.

Sampling

Patients aged 18-64 years were selected based on stratified random sampling. All patients provided written informed consent. Those with mental retardation, neurodegenerative disorders, and insufficient Finnish language skills were excluded. Of 1361 eligible patients, 610 declined to participate and 304 were lost for other reasons, yielding a total number of participants of 447 and a response rate of 33%. The final number of patients for this study was 400, as 47 patients with a principal diagnosis of anxiety disorder, eating disorder, neuropsychiatric disorder, or substance use disorder were subsequently excluded due to the low numbers of subjects in each group.

Diagnostic assessment

Diagnostic assessments were performed according to the International Classification of Disease, 10th revision, Diagnostic Criteria for Research (ICD-10-DCR) [27] following the principle of lifetime diagnosis. Using all available outpatient records, the authors (K.A., I.B., M.K., and B.K.) re-examined clinical diagnoses originally given by attending psychiatrists. We formed three subgroups according to the most common principal diagnoses: schizophrenia or schizoaffective disorder (SSA, n=113), bipolar disorder (BD, n=99), and depressive disorders (DD, n=188). In addition, any substance use disorder (SUD) was classified as a secondary clinical diagnosis.

Specialized psychiatric outpatient care in Finland

The Psychiatry Outpatient Clinics in Finland offer specialized outpatient care. Patients require a referral from another healthcare provider. Visits to the clinic are by appointment and are free of charge to the patient. The clinics have a multidisciplinary staff comprising psychiatrists, nurses, psychologists, social workers, and, in many clinics, occupational therapists.

Self-reported assessment of treatment adherence

Patients were asked to assess their adherence to outpatient visits and to psychiatric pharmacotherapy by the question “how often during the current treatment have you attended outpatient visits/used the

prescribed psychiatric medication?" Response options were given on a scale from zero (never) to three (regularly). Current inpatients replied on attendance of outpatient visits beyond the period of hospitalization. Patients ranked their attitude to outpatient visits and medication on a scale from zero (negative) to three (highly positive). Furthermore, patients assessed their satisfaction with current psychiatric outpatient treatment (from unsatisfied to highly satisfied) and motivation for treatment (low-moderate-high). We used original questionnaires on adherence and attitude from large screening-based studies [21,22] from same catchment area to ensure the comparability of methodology. Furthermore, available measurements of adherence comprise only psychopharmacology and/or validated for certain mental disorders.

Other measures

The Beck Depression Inventory (BDI) [28] is a self-report questionnaire for measuring the severity of depression symptoms. The Overall Anxiety Severity and Impairment Scale (OASIS) [29] is a self-report questionnaire to assess severity and impairment associated with anxiety. The OASIS includes five questions regarding the frequency and severity of anxiety symptoms as well as anxiety-related avoidance behavior and decreased functioning at home/work/school and in social life. The McLean Screening Instrument for Borderline Personality Disorder (MSI) [30] is a self-report questionnaire for screening for borderline personality disorder. The Alcohol Use Disorders Identification Test (AUDIT) [31] is a self-report questionnaire to assess alcohol consumption, alcohol dependence symptoms, and alcohol-related problems. All of these scales have at least good internal consistency (Cronbach's alpha for BDI 0.91; OASIS 0.84; MSI 0.92; AUDIT 0.90).

Statistical analyses

Ordinal variables of treatment adherence (visits and pharmacotherapy) were analysed as four-level ordinal variables, but also recoded into dichotomous variables of "adherent/non-adherent". We included in the "adherent to visits" group those patients who reportedly attended outpatient appointments regularly or partly regularly, as such frequency would enable implementation of the treatment program. The group of "adherent to pharmacotherapy" included only patients who reported using their medication regularly. Secondary diagnoses of SUD were used in statistical analyses as a dichotomous nominal variable (absence or presence of SUD diagnosis). Duration of treatment was calculated from the date of first request of psychiatric specialized care.

In bivariate analyses, we used T-test or ANOVA to investigate the relationships between nominal/ordinal and continuous normally distributed variables, and Mann-Whitney U-test or Kruskal-Wallis test in case of skewed distributions. Relationships between nominal and/or ordinal variables were tested with Chi-square test; in case of small sample size, Fisher's exact test was used. The variables clustered into groups, representing socio-demographics (age, gender, marital status, cohabitation status, education), course of illness (number of hospitalizations), current symptoms and comorbid states (depressive, anxiety, and borderline personality symptoms, diagnosis of SUD), and attitude to treatment (outpatient visits and

medication). Variables associated with adherence to treatment most consistently across all diagnostic groups in bivariate analyses were included in logistic regression analyses. Statistical significance was set at $p<0.05$. These variables were treatment setting (hospital, outpatient unit) and diagnosis of SUD. In addition, not correlated but clinically relevant variables of sex and age were included in the analyses. The main regression model was built with all variables. Additionally, we performed regression analyses excluding treatment setting, as treatment in hospital could be a consequence of poor treatment adherence. Statistical analysis was performed using the Statistical Package for the Social Sciences [32].

Results

Socio-demographic and background data

The majority of BD and DD patients were females; in the SSA group, sex distribution was nearly equal ($p<0.001$) (Table 1). Compared with mood disorder groups, SSA patients were more often unmarried and living alone ($p<0.001$). Subjects with BD had comorbid SUD more often than other patients ($p=0.001$). The SSA group had the highest proportion of inpatients ($p=0.018$), and its patients had required hospitalizations more often than patients with BD and DD ($p<0.001$).

Adherence and attitude to treatment

In total, the vast majority (78.5%) of patients reported having attended outpatient visits regularly or partly irregularly. Non-adherence to outpatient visits was significantly more common in inpatients than in outpatients across all groups ($p<0.001$) (Table 2). Inpatients had a long-term mental care background, as mean overall duration (in years) of specialized psychiatric treatment was 21.9 in SSA, 11.4 in BD, and 8.8 in DD groups. Of non-adherent inpatients, in 94% of SSA, 85% of BD, and 79% of DD patients, psychiatric treatment had continued for over one year.

A high proportion of the patients (79.2%) had reported regular use of prescribed psychiatric medication (table 2). Also, 72.8% of SSA, 77.9% of BD, and 82.0% of DD patients were positive or highly positive about their outpatient visits. The corresponding figures for attitude to medication were 70.0%, 71.8%, and 58.3%. Patients in all groups were mostly satisfied with psychiatric treatment and declared a strong treatment motivation.

Relationships between treatment adherence and other variables

Subjects with SSA and DD who reported themselves adherent to outpatient visits had needed significantly less often hospital treatment than their non-adherent counterparts ($p=0.021$ and $p<0.001$, respectively). Patients with a diagnosis of SUD attended outpatient visits less often than those without this diagnosis in all groups (Table 3). Moreover, adherence to visits was significantly poorer in inpatients with SUD than in outpatients with SUD ($p<0.001$ in SSA, $p=0.001$ in BD, and $p=0.007$ in DD). SSA patients who were adherent

to outpatient visits had significantly higher OASIS scores (p=0.029), and DD patients lower OASIS scores (p=0.004), than their non-adherent counterparts. DD patients with poor adherence to visits had higher MSI scores (p=0.040), and BD and DD patients with poor adherence had higher AUDIT scores (both, p=0.010), than adherent patients. Treatment adherence weakly directly correlated with treatment satisfaction in the SSA (r=0.285, p=0.003) and BD (r=0.255, p=0.011).

Regression analyses

Treatment setting was most strongly and consistently associated with adherence to outpatient visits across all diagnostic groups (Table 4). The diagnosis of SUD had a regression weight in the main model in SSA and DD patients, and in all diagnostic groups in the additional analyses.

Discussion

This study investigated self-reported treatment adherence in psychiatric in- and outpatients from different perspectives, including adherence and attitude to outpatient treatment and to pharmacotherapy. Overall, most patients reported positive attitudes to any form of treatment and regular use of their medication. However, irrespective of diagnosis, current outpatients had been clearly more adherent to preceding outpatient visits than current inpatients. Indeed, hospital setting was the strongest clinical correlate of poor adherence in all diagnostic groups. Substance use disorder was another significant contributor to non-adherence in all three groups.

Overall adherence and attitude to psychiatric treatment.

Based on self-reports, more than two-thirds of all patients were satisfied with and motivated for psychiatric treatment. In addition, the vast majority of all patients had reported a positive attitude to both outpatient visits and medication. Along with positive attitude, 71.7-83.7% of all patients reported regular use of psychiatric medication. This result is in line with previous studies, demonstrating overall high (52.5-77.9%) self-report adherence to psychopharmacotherapy [21,22,33,34]. However, such subjective compliance is often contradicted by objectively measured compliance (serum levels, pill counts, etc.), in which actual adherence has been as low as 34-50% [17,35,36]. Thus, while some authors find self-report questionnaires to be a reliable measurement of compliance to psychopharmacotherapy [37], the use of objective methods may increase accuracy of detecting adherence problems, and therefore, may be beneficial in preventing relapses and hospitalizations [15,35]. Overall, our findings emphasize that regardless of principal mental disorder, patients likely have a positive attitude to treatment and the intention of regularly using their medication. Thus, it is important to maintain such attitude, however, considering disorder-specific treatment challenges.

Self-report adherence to outpatient visits

Our study enabled us to compare AT between in- and outpatients, and these groups differed markedly. The majority of our patients were recruited into the study from outpatient units. These patients were clearly more adherent to outpatient visits than subjects recruited from hospitals. In particular, more than half of all inpatients in all groups reported never attending treatment visits, despite the vast majority of them having utilized specialized psychiatric care for years. Such remarkable differences between treatment settings in treatment adherence were confirmed in regression analyses for all diagnostic groups. Although establishing causal relationships is not possible, this phenomenon could be considered from different perspectives. Hospitalization is naturally associated with a more severe course of illness, which in some studies has been demonstrated to be a contributor to non-adherence [17,21,22]. In turn, lack of involvement in outpatient care results in insufficient treatment of mental disorders, causing an increased need of hospitalization [38]. In addition, sometimes non-attendance of outpatient visits results from high cost or deficient availability, of such treatment form [39,40]. However, for public specialized psychiatric care patients of the Helsinki region this is unlikely to apply since such patients (at least those suffering from major MDs) have the opportunity for regular and free-of-charge outpatient care.

Another strong contributor to non-adherence to outpatient visits was a substance use disorder (SUD). This finding is consistent with previous studies demonstrating a significant role of substance use in overall non-adherence to psychiatric treatment, including medication, psychotherapy, and psychosocial methods [17,18,20,21]. Along with this disorder-related factor, poor adherence to treatment might include other elements as well. First, in addition to the generally negative impact of self-stigmatization on treatment compliance [41], patients with substance abuse are often stigmatized by healthcare professionals [42,43], which could lead to feeble treatment alliance and subsequent poor treatment adherence. Moreover, psychiatric care and treatment of substance abuse are often divided into separate services, which it also true in Finland. This healthcare system could restrict the availability of psychiatric treatment for MD patients with substance abuse comorbidity.

Interestingly, the proportions of non-adherent SUD patients in all diagnostic groups were much higher among inpatients than outpatients. We assume that within our sample there is a group of SUD patients who neglect outpatient care and utilize psychiatric services only in the form of hospitalizations. This assumption could be partly affirmed by the finding that the vast majority of our inpatients have a long-term mental care history. Although such non-adherent SUD inpatients are few in number, they are likely to form a therapeutically challenging group with a high risk of negative outcome. As life expectancy of psychiatric patients is 10-20 years shorter than in the general population [44,45], both poor adherence and substance abuse contribute to this by worsening the course of MD (prominent relapses or lack of remission) [6,7,46] and intensifying suicidal behaviour [9,47]. Additionally, inadequate outpatient treatment causes accumulating health and social problems, which eventually result in prolonged hospital treatment, increasing healthcare costs [7,11].

In summary, it is important to identify patients with substance abuse in routine clinical practice, as these patients are at high risk of discontinuing psychiatric treatment. Such risk is probably more prominent for the patients using hospital treatment rather than outpatient care. Thus, in addition to careful diagnostic assessment (including SUD comorbidity), the clinician should identify a patient´s non-adherence to outpatient care and, if necessary, enhance treatment compliance using motivational techniques [3,48]. Also, patients could benefit from a closer collaboration between psychiatric care and substance abuse services.

Strengths and limitations

The main strength of this study is the multi-factorial investigation of adherence to treatment simultaneously in bipolar, depressive, and schizophrenia spectrum disorders within a relatively large (N=400) sample. Along with psychopharmacotherapy, the study explores in detail the background factors of adherence to outpatient visits, which is often beyond the focus of related studies. Furthermore, this study compares adherence to treatment within clinically important subsamples of in- and outpatients.

The study also had some limitations. First, this study included a long survey and was performed in a busy clinical practice, which resulted in a relatively low response rate of 33%. We do not, however, expect any obvious selection bias, as register-based analysis of representativeness showed no difference from the patient populations of participating organizations in terms of age or gender. Other demographic characteristics were consistent with the large screening-based Vantaa Depression Study and Jorvi Bipolar Study [49,50]. Furthermore, in investigation of treatment adherence high proportion of drop-outs could refer to selection bias. However, we assume that use of anonymous self-reports likely diminished patients' threshold to disclose adherence problems. Second, we did not collect any objective information on attendance of outpatient treatment or medication use from medical records. Second, determination of any causal relationships for treatment adherence was not possible in a cross-sectional study. Third, both diagnoses of principal disorder and substance use were not based on structured interviews, although they were validated by the authors based on medical records. Fifth, the study included multiple statistical analyses arising issue of multiple testing. However, regression models were used as main test, while other analyses were mostly descriptive.

Overall, common features emerge from self-reported adherence to psychiatric treatment in patients with schizophrenia or schizoaffective disorder, bipolar disorder, and depression. The majority of patients are reportedly highly motivated and have a positive attitude to psychopharmacological and outpatient treatment. Non-adherence to outpatient visits is associated with hospital treatment and substance use disorders. Careful detection of adherence issues is essential in every treatment setting, but especially important among inpatients. Furthermore, regardless of the principal mental disorder, it is necessary to recognize substance abuse to enhance treatment adherence and ensure proper treatment. Substance use-related non-adherence to treatment could be mitigated by close collaboration between psychiatric care and substance abuse services.

References

1. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. Therapeutics and Clinical Risk Management. 2008 Feb;4(1):269-86.
2. Thompson L, McCabe R. The effect of clinician-patient alliance and communication on treatment adherence in mental health care: a systematic review. BMC Psychiatry. 2012 Jul 24;12:87.
3. Joosten EA, DeFuentes-Merillas L, de Weert GH, Sensky T, van der Staak CP, de Jong CA. Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status. Psychotherapy and Psychosomatics. 2008;77(4):219-26.
4. Sabaté E. Adherence to long-term therapies: evidence for action. World Health Organization; 2003.
5. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatrica Scandinavica. 2002 Mar;105(3):164-72.
6. Marder SR. Overview of partial compliance. Journal of Clinical Psychiatry. 2003;64 Suppl 16:3-9.
7. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization a mong CaliforniaMedicaid patients with schizophr enia. Psychiatric Services. 2004 Aug;55(8):886-91.
8. Colom F, Vieta E, Tacchi MJ, Sánchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. Bipolar Disorders. 2005;7 Suppl 5:24-31.
9. Meehan J, Kapur N, Hunt IM, et al. Suicide in mental health in-patients and within 3 months of discharge. National clinical sur vey. British Journal of Psychiatry. 2006 Feb;188:129-34.
10. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medic ation and health care costs among Medicaid beneficiaries with schizoph renia. American Journal of Psychiatry. 2004 Apr;161(4):692-9.
11. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. Psychiatric Services. 2001 Jun;52(6):805-11.
12. Hearnshaw H, Lindenmeyer A. What do we mean by adherence to treatment and advice f or living with diabetes? A review of the literature on definitions and measurements. Diabetic Medicine. 2006 Jul;23(7):720-8.
13. Haynes RB, Sackett DL. Compliance with therapeutic regimens. Johns Hopkins University Press; 1976
14. Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. Journal of Psychosomatic Research. 2010 Dec;69(6):591-9.
15. Velligan DI, Weiden PJ, Sajatovic M, et al.; Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. Journal of Clinical Psychiatry. 2009;70 Suppl 4:1-46; quiz 47-8.
16. Murru A, Pacchiarotti I, Amann BL, Nivoli AM, Vieta E, Colom F. Treatment adherence in bipolar I and schizoaffective disorder, bipolar type. Journal of Affective Disorders. 2013 Dec;151(3):1003-8.
17. Leclerc E, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipol ar disorder: a comprehensive review. Journal of Affective Disorders. 2013 Jul;149(1-3):247-52.
18. Czobor P, Van Dorn RA, Citrome L, Kahn RS, Fleischhacker WW, Volavka J. Treatment adherence in schizophrenia: a patient-level meta-analysis of combined CATIE and EUFEST studies. European Neuropsychopharmacology. 2015 Aug;25(8):1158-66.
19. Gibson S, Brand SL, Burt S, Boden ZV, Benson O. Understanding treatment non-adherence in schizophrenia and bipolar disorder:

a survey of what service users do and why. BMC Psychiatry. 2013 May 29;13:153.

20. Demyttenaere K. Risk factors and predictors of compliance in depressio n. European Neuropsychopharmacology.. 2003 Sep;13 Suppl 3:S69-75.
21. Holma IA, Holma KM, Melartin TK, Isometsä ET. Treatment attitudes and adherence of psychiatric patients with major depressive disorder: a five-year prospective study. Journal of Affective Disorders. . 2010 Dec;127(1-3):102-12.
22. Arvilommi P, Suominen K, Mantere O, Leppämäki S, Valtonen H, Isometsä E. Predictors of adherence to psychopharmacologic al and psychosocial treatment in bipolar I or IIdisorders - an 18-month prospective study. Journal of Affective Disorders. 2014 Feb;155:110-7.
23. Gray R, Bressington D, Ivanecka A, et al. Is adherence therapy an effective adjunct treatment for patients with schizophrenia spectrum disorders? A systematic review and meta-analysis. BMC Psychiatry. 2016 Apr 6;16:90.
24. Coodin S, Staley D, Cortens B, Desrochers R, McLandress S. Patient factors associated with missed appointments in persons with schizophrenia. Canadian Journal of Psychiatry. 2004 Feb;49(2):145-8.
25. Aaltonen K, Näätänen P, Heikkinen M, et al. Differences and similarities of risk factors for suicidal ideation and attempts among patients with depressive or bipolar disorders. Journal of Affective Disorders. 2016; 193:318-30.
26. Karpov B, Joffe G, Aaltonen K, et al. Anxiety symptoms in a major mood and schizophrenia spectrum disorders. European Psychiatry. 2016; 37:1-7.
27. World Health Organization. International classification of disease, 10th ed., Geneva; 1992.
28. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of General Psychiatry. 1961; 4:561-571.
29. Norman SB, Cissell SH, Means-Christensen AJ, Stein MB. Development and validation of an Overall Anxiety Severity and Impairment Scale (OASIS). Depression and Anxiety. 2006; 23(4):245–249.
30. Zanarini MC, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J. A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). Journal of Personality Disorders. 2003; 17(6):568-573.
31. Babor TF, Saunders J, Grant M. AUDIT: The Alcohol Use Disorder Identification Test: Guidelines for Use in Primary Health Care. World Health Organization. Geneva, Switzerland. 1992.
32. IBM SPSS Statistics for Windows, Version 22.0. Released 2013. Armonk, NY: IBM Corp.
33. Rettenbacher MA, Hofer A, Eder U, et al. Compliance in schizophrenia: psychopathology, side effects, and patients' attitudes toward the illness and medication. Journal of Clinical Psychiatry. 2004 Sep;65(9):1211-8.
34. De Las Cuevas C, Peñate W. Explaining pharmacophobia and pharmacophilia in psychiatric patients: relationship with treatment adherence. Human Psychopharmacology. 2015 Sep;30(5):377-83.
35. Yalcin-Siedentopf N, Wartelsteiner F, Kaufmann A, et al. Measuring adherence to medication in schizophre nia: the relationship between attitudes toward drug therapy and plasma levels of new-generation antipsychotics. International Journal of Neuropsychopharmacology. 2014 Dec 7;18(5).
36. Sajatovic M, Levin JB, Sams J, et al. Symptom severity, self-reported adherence, and electronic pill monitoring in poorly adherent patients with bipolar disorder. Bipolar Disorders. 2015 Sep;17(6):653-61.
37. Jónsdóttir H, Opjordsmoen S, Birkenaes AB, et al. Medication adherence in outpatients with severe mental disorders: relation between self-reports and serum level. Journal of Clinical Psychopharmacology. 2010 Apr;30(2):169-75.
38. Grinshpoon A, Lerner Y, Hornik-Lurie T, Zilber N, Ponizovsky AM. Post-discharge contact with mental health clinics and psychiatric readmission: a 6-month follow-up

study. Israel Journal of Psychiatry and Related Sciences. 2011;48(4):262-7.

39. Saxena S, Thornicroft G, Knapp M, Whiteford H. Resources for mental health: scarcity, inequity, and inefficiency. Lancet. 2007 Sep 8;370(9590):878-89.
40. Malowney M, Keltz S, Fischer D, Boyd JW. Availability of outpatient care from psychiatrists: a simulated-patient study in three U.S. cities. Psychiatric Services. 2015 Jan 1;66(1):94-6.
41. Fung KM, Tsang HW, Corrigan PW. Self-stigma of people with schizophrenia as predictor of their adherence to psychosocial treatment. Psychiatric Rehabilitation Journal. 2008 Fall;32(2):95-104.
42. Room R. Stigma, social inequality and alcohol and drug use. Drug and Alcohol Review. 2005; 24(2):143-55.
43. Keyes KM, Hatzenbuehler ML, McLaughlin KA, Link B, Olfson M, Grant BF, et al. Stigma and treatment for alcohol disorders in the United States. American Journal of Epidemiology. 2010; 172(12):1364-72.
44. Walker ER, McGee RE, Druss BG. Mortality in mental
disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry. 2015; 72(4):334-41.
45. Wahlbeck K, Westman J, Nordentoft M, Gissler M, Laursen TM. Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. British Journal of Psychiatry. 2011; 199(6):453-8.
46. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry. 2005; 62(6):593-602.
47. Yuodelis-Flores C, Ries RK. Addiction and suicide: A review. American Journal of Addictions. 2015; 24(2):98-104.
48. Chien WT, Mui JH, Cheung EF, Gray R. Effects of motivational interviewing-based adherence therapy for schizophrenia spectrum disorders: a randomized controlled trial. Trials. 2015 Jun 14;16:270.
49. Melartin TK, Rytsala HJ, Leskela US, Lestela-Mielonen PS, Sokero TP, Isometsa ET. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. Journal of Clinical Psychiatry. 2002; 63(2):126 – 134.
50. Mantere O, Suominen K, Leppämäki S, Valtonen H, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). Bipolar Disorders. 2004; 6(5):395-405.

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Conflict of interests

The authors declare that there is no conflict of interest.

Table 1. Socio-demographic and clinical characteristics.

	SSA		BD		DD		Total		p-value
	n	%	n	%	n	%	n	%	
Number	113	28.3	99	24.8	188	46.9	400	100.0	
Female	54	47.8	63	63.6	146	77.7	263	65.8	<0.001[1]
Marital status									<0.001[1]
Married/cohabitating	10	9.1	37	37.4	68	36.6	115	29.1	
Divorced/widowed	19	17.3	30	30.3	39	21.0	88	22.3	
Unmarried	81	73.6	32	32.3	79	42.4	192	48.6	
Cohabitation status									<0.001[1]
Single	63	57.3	36	36.4	77	41.4	176	44.6	
Cohabitating	22	20.0	51	51.5	95	49.1	168	42.5	
Residential communities/ other	25	22.7	12	12.1	14	7.5	51	12.9	
Vocational education	68	61.8	71	71.7	121	65.1	260	65.8	0.307[1]
University	18	16.4	22	22.2	30	16.1	70	17.7	
SUD diagnosis	35	31.0	38	38.4	36	19.1	109	27.3	0.001[1]
Treatment setting									0.018[1]
Outpatients	77	68.1	79	79.8	154	81.9	310	77.5	
Inpatients	36	31.9	20	20.2	34	18.1	90	22.5	
Age, mean (SD)	44.3 (12.4)		43.4 (12.3)		41.2 (13.3)		42.0 (13.0)		0.002[2]
Number of hospitalizations, mean (SD)	2.0 (1.1)		1.5 (1.3)		0.9 (1.2)		1.4 (1.3)		<0.001[2]

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder

SUD = substance use disorder

[1] Chi-square test, [2] Kruskall-Wallis test (between-group comparison)

Table 2. Adherence and attitude to psychiatric outpatient care.

	SSA (n = 113)		BD (n = 99)		DD (n = 188)		p-value[1]
	n	%	n	%	n	%	
Attendance of outpatient visits							
Inpatients							0.145
Never	18	52.9	12	60.0	17	51.5	
Irregular	2	5.9	3	15.0	4	12.1	
Partly irregular	3	8.8	2	10.0	3	9.1	
Regular	13	32.4	3	15.0	10	27.3	
Outpatients							0.254
Never	8	10.5	3	3.8	9	5.9	
Irregular	2	2.6	3	3.8	2	1.3	
Partly irregular	16	21.1	17	21.5	28	18.4	
Regular	50	65.8	56	70.9	113	74.3	
Attitude to outpatient visits							0.235
Negative	1	1.0	4	4.3	3	1.6	
Neutral	27	26.2	17	17.9	30	16.3	
Positive	41	39.8	45	47.4	81	44.1	
Highly positive	34	33.0	29	30.4	70	38.0	
Use of psychiatric pharmacotherapy							0.091
Never	1	0.9	1	1.0	6	3.3	
Irregular	2	1.8	4	4.0	1	0.5	
Partly irregular	15	13.6	23	23.3	29	15.6	
Regular	92	83.7	71	71.7	150	80.6	
Attitude to psychiatric pharmacotherapy							0.088
Negative	14	12.7	9	9.1	24	12.8	
Neutral	19	17.3	19	19.2	54	28.9	
Positive	52	47.3	55	55.6	81	43.3	
Highly positive	25	22.7	16	16.1	28	15.0	
Satisfaction with treatment							0.401
Dissatisfied	10	9.0	8	8.1	17	9.1	
Neutral	24	21.6	17	17.2	35	18.7	
Satisfied	59	53.2	51	51.5	91	48.7	
Highly satisfied	18	16.2	23	23.2	44	23.5	
Motivation to treatment							0.280
Low	7	6.3	1	1.0	2	1.1	
Moderate	17	15.3	16	16.2	36	19.3	
High	87	78.4	83	83.8	149	79.6	

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder
[1] Kruskal-Wallis test

Table 3. Diagnosis of SUD through the items of adherence to outpatient visits by diagnostic groups.

	SSA (n = 113)				BD (n = 99)				DD (n = 188)			
	SUD		No SUD		SUD		No SUD		SUD		No SUD	
	n	%	n	%	n	%	n	%	n	%	n	%
Adherence to outpatient visits (inpatients)												
Irregular	11	91.7	9	40.9	10	71.4	5	83.3	13	72.2	8	53.3
Regular	1	8.3	13	59.1	4	28.6	1	16.7	5	27.8	7	46.7
	p=0.009[1]				p=0.517[1]				p=0.261[1]			
Adherence to outpatient visits (outpatients)												
Irregular	5	23.8	5	9.1	4	16.7	2	3.6	4	23.5	7	5.2
Regular	16	76.2	50	90.9	20	83.3	53	96.4	13	76.5	128	94.8
	p=0.090[1]				p=0.066[1]				p=0.022[1]			
Adherence to outpatient visits (total)												
Irregular	16	48.5	14	18.2	14	36.8	7	11.5	17	48.6	15	10.0
Regular	17	51.5	63	81.8	24	63.2	54	88.5	18	51.4	135	90.0
	p=0.002[2]				p=0.005[2]				p<0.001[2]			

SUD = substance use disorder
SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder
[1] Fisher´s exact test; [2] Chi-square test

Table 4. Logistic regression analysis of clinical correlates for adherence to outpatient visits within diagnostic groups.

	SSA (n = 113)			BD (n = 99)			DD (n = 188)		
	B	Exp (B)	Sig.	B	Exp (B)	Sig.	B	Exp (B)	Sig.
Main model									
Sex	0.191	1.210	0.721	0.221	1.247	0.745	-0.594	0.552	0.348
Age	-0.007	0.993	0.729	-0.011	0.989	0.701	-0.007	0.993	0.688
Hospital treatment	**-2.418**	**11.226**	**0.000**	**-3.417**	**30.479**	**0.000**	**-2.766**	**15.889**	**0.000**
SUD	**-1.686**	**5.398**	**0.003**	-0.720	2.055	0.297	**-1.380**	**3.976**	**0.012**
Additional model									
Sex	0.148	0.862	0.749	0.055	0.947	0.919	-0.254	0.775	0.3623
Age	-0.023	0.977	0.219	0.004	1.004	0.701	0.011	1.011	0.529
SUD	**-1.555**	**4.733**	**0.001**	**-1.535**	**4.643**	**0.006**	**-2.258**	**9.560**	**0.000**

SSA = schizophrenia or schizoaffective disorder; BD = bipolar disorder; DD = depressive disorder
SUD = Substance Use Disorder diagnosis

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Original article

Level of functioning, perceived work ability, and work status among psychiatric patients with major mental disorders

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ABSTRACT

Background: Major mental disorders are highly disabling conditions that result in substantial socioeconomic burden. Subjective and objective measures of functioning or ability to work, their concordance, or risk factors for them may differ between disorders.
Methods: Self-reported level of functioning, perceived work ability, and current work status were evaluated among psychiatric care patients with schizophrenia or schizoaffective disorder (SSA, $n = 113$), bipolar disorder (BD, $n = 99$), or depressive disorder (DD, $n = 188$) within the Helsinki University Psychiatric Consortium Study. Correlates of functional impairment, subjective work disability, and occupational status were investigated using regression analysis.
Results: DD patients reported the highest and SSA patients the lowest perceived functional impairment. Depressive symptoms in all diagnostic groups and anxiety in SSA and BD groups were significantly associated with disability. Only 5.3% of SSA patients versus 29.3% or 33.0% of BD or DD patients, respectively, were currently working. About half of all patients reported subjective work disability. Objective work status and perceived disability correlated strongly among BD and DD patients, but not among SSA patients. Work status was associated with number of hospitalizations, and perceived work disability with current depressive symptoms.
Conclusions: Psychiatric care patients commonly end up outside the labour force. However, while among patients with mood disorders objective and subjective indicators of ability to work are largely concordant, among those with schizophrenia or schizoaffective disorder they are commonly contradictory. Among all groups, perceived functional impairment and work disability are coloured by current depressive symptoms, but objective work status reflects illness course, particularly preceding psychiatric hospitalizations.

1. Introduction

According to Global Burden of Disease Study, mental disorders (MDs) are highly disabling conditions [1,2]. Moreover, same study demonstrates that poor functioning (measured in years lived with disability and disability-adjusted life years), leading to weak labour engagement of people with MDs [3,4], has resulted in an increased socioeconomic burden of MDs [5]. In addition to generally reduced employment [4], subjects with MDs have more difficulties in returning to work after sick leave [6–8] and tend to retire earlier [9,10] than the general population.

More specifically, major depressive disorder, bipolar disorder, and schizophrenia, along with anxiety disorders, are among the greatest contributors to the global burden of MDs [3]. Furthermore, depression is among the ten most disabling diseases worldwide [1,11]. However, most persons with depression and bipolar disorder manage to maintain employment status [12,13]. The accumulating vocational impairment is more severe in bipolar disorder than in depression, and the difference tends to grow over time [14]. In contrast to mood disorders, only about 20% of subjects with schizophrenia remain employed [15–17]. Interestingly, current labour status is often discordant with perceived work disability. Many authors have demonstrated that subjects with

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depression and, to some extent, bipolar disorder tend to overestimate their impairment in work ability [18–20], while subjects with schizophrenia spectrum disorders may underestimate it [21,22].

In addition to prevalence, the risk factors for MD-related disability have been extensively studied. Many general population and clinical sample studies demonstrate roughly similar associations of functional impairment and work disability in depression, bipolar disorder, and schizophrenia with numerous socio-demographic and clinical factors. These include, for instance, older age [23–25], duration and number of hospitalizations [26,15], educational level [23,25], and severity of current affective symptoms [22,24,27,28]. However, few clinical studies [29] have investigated functional impairment and its predictors concurrently in depression, bipolar disorder, and schizophrenia spectrum disorder within the same sampling frame and with similar methods. Therefore, similarities and differences between risk factors remain partly unclear. Moreover, we are not aware of studies investigating correlations between subjective and objective work disability across different mental disorders. Most studies on predictors of functional impairment in major mental disorders have investigated the impact of disorder-related symptoms (neurocognitive, affective, psychotic) [17,29–31]. Other clinical or psychological traits, e.g. comorbid borderline personality features and level of self-efficacy, may also considerably influence functioning [32–34].

We aimed, first, to investigate perceived level of functioning and ability to work and objective work status within a cohort of psychiatric care patients with either schizophrenia or schizoaffective disorder, bipolar disorder, or depressive disorder. We expected notable functional impairment in all patients, with the most severe disability in the schizophrenia or schizoaffective disorder group. Second, we investigated associations of functioning and work ability with putative risk factors regarding preceding course (age at onset, number of hospitalizations) and current state of illness (affective symptoms) as well as clinical and psychopathological variables (self-efficacy, borderline personality traits). We hypothesized that correlates of functioning and work disability would be broadly similar across groups, but concordance between subjective and objective measures would be lower among patients with schizophrenia spectrum disorders.

2. Methods

2.1. Setting

The methodology of the Helsinki University Psychiatric Consortium (HUPC) study has been presented in detail in the authors' previous reports [35–37] and is only briefly outlined below.

The HUPC study was carried out in secondary mental health services, including 10 community mental health centres, in 24 psychiatric inpatient units, in one day-care hospital, and in two residential communities of the Helsinki metropolitan area in 2011–2012. The study was approved by the Ethics Committee of Helsinki University Central Hospital.

2.2. Sampling

Inclusion criteria were age of 18 to 64 years and provision of written informed consent.

Patients were randomly drawn from all eligible patients, stratified by setting. Patients with mental retardation, neurodegenerative disorders, or insufficient Finnish language skills were excluded. We recruited only patients, whose condition was stable enough to allow responding to the questionnaires. Of 1361 eligible patients, 610 declined to participate and 304 were lost for other reasons. The final number of participants was 447, resulting in a response rate of 33%. In addition, 47 patients with a principal diagnosis of anxiety disorder, eating disorder, neuropsychiatric disorder, or substance use disorder were excluded from the current study, leaving 400 participants.

2.3. Diagnostic assessment

The principal clinical diagnoses given by attending psychiatrists were re-examined by the authors (K.A., I.B., M.K., and B.K.) following the criteria of the International Classification of Disease, 10th revision, Diagnostic Criteria for Research [38]. For the current study, patients were divided into three subgroups: schizophrenia or schizoaffective disorder (SSA, $n = 113$), bipolar disorder (BD, $n = 99$), and depressive disorders (DD, $n = 188$).

2.4. Measure of functional impairment

The Sheehan Disability Scale (SDS) [39,40] is a three-item self-report scale to assess functional impairment on three domains: work, social life or leisure activities, and home life or family responsibilities. Each item is scored from zero to 10. The three items can be summed into a single dimensional scale of global functional impairment ranging from zero (no impairment) to 30 (high impairment). The SDS has no recommended cut-off score. However, a score of five and more on any of the scales is considered to indicate significant functional impairment.

2.5. Other measures

The Beck Depression Inventory (BDI) [41] is a self-report questionnaire for measuring the severity of depression symptoms. The Overall Anxiety Severity and Impairment Scale (OASIS) [42] is a self-report questionnaire to assess severity and impairment associated with anxiety. The General Self-Efficacy Scale (GSE) [43] is a self-report instrument to assess perceived self-efficacy regarding stressful life events. The McLean Screening Instrument for borderline personality disorder (MSI-BPD, hereafter MSI) [44] is a self-report questionnaire for screening for borderline personality disorder. All the scales had at least good internal consistency (Cronbach's alpha for total SDS 0.80; OASIS 0.84; BDI 0.91; GSE 0.93; MSI 0.92).

2.6. Assessment of work status and ability to work

In Finland, disability pension could be granted after 300 days of sick leave in a two-year period if the person was still considered unable to work or find employment that fits person's vocational qualifications because of an illness. That also applies to people working in a household. The Social Insurance Institution of Finland or other pension providers grant a pension based on the person's current and expected functional level presented in medical certificates of the attending physician. The authors collected information from medical records and certificates (for sick leave or disability pension) on a patient's current work/employment status, creating a three-item nominal variable (working, sick leave, or disability pension/rehabilitation subsidy). For further analyses, this variable was modified to a dichotomous as working and not-working (sick leave and disability pension/rehabilitation subsidy).

Patients were asked about their perceived ability to work, producing ordinal variable: 1 – able to work, 2 – reduced work ability, 3 – unable to work. For further analyses, this variable was transformed into the dichotomous form of able to work (items 1 and 2 combined)/unable to work. This categorization has been used also in previous studies [23,24]. Data on ability to work (work

status) gathered from medical records were designated as "objective" and from patients as "subjective".

2.7. Statistical analyses

Relationships between nominal variables were tested with Chi^2 test and between nominal/ordinal and continuous variables with Mann–Whitney U-test or Kruskal–Wallis test. The variables represented domains of demographics (age, gender), societal status (marital status, number of children, education), course of disease (age at onset, number of hospitalizations), and current symptoms (depressive, anxiety, borderline personality symptoms, self-efficacy). In case of skewed distributions, we used non-parametric tests. The relationships between total SDS and other continuous variables (age, age at onset, number of hospitalizations, measurement scales) were tested with Spearman's bivariate correlation analysis (BCA). Variables associated with SDS and work ability most consistently across all diagnostic groups in univariate analyses were included in regression analyses. Thus, linear regression models were built to estimate the associations between total SDS and measures that correlated with it in BCA. These measures were BDI, OASIS, and GSE. Also, the not correlated but clinically relevant variables of age, age at onset, number of hospitalizations, and duration of treatment were included in the regression analyses. The same logic was applied in logistic regression models to investigate associations between objective and subjective ability to work. Thus, the regression model included age, age at onset, number of hospitalizations, BDI, OASIS, GSE, and SDS. To avoid cross-loading of two different self-report work ability measures, we excluded the work domain from the total SDS variable. Thus, SDS was included in the analysis as a measure of other functioning, not work-related. Relationships of objective (ordinal variable of work status) and subjective work ability (initial ordinal variable) within diagnostic groups were explored with Spearman's bivariate correlation analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences [45].

3. Results

3.1. Socio-demographic and background data

Patients in all diagnostic groups were middle-aged and, with the exception of the SSA group, mainly women (Table 1). The SSA group had the highest number of unmarried and childless patients across all groups ($P < 0.001$). Most patients had a professional education. Subjects with BD had comorbid alcohol use disorders (AUDs) more often than other patients ($P = 0.012$). The mean age at onset of the principal disorder was seemingly the same across diagnostic groups, being, however, significantly lowest in SSA patients ($P = 0.006$). These patients also had a longer history of treatment and a higher number of hospitalizations than their mood disorder counterparts ($P < 0.001$). DD patients had significantly higher scores on BDI and OASIS and lower scores on GSE scales than BD or SSA patients.

3.2. Self-reported functioning on the Sheehan Disability Scale

Of all diagnostic groups, subjects with DD collected the highest and subjects with SSA the lowest scores on SDS in all three domains (Table 2). The mean scores on each of the three scales exceeded five in all groups (except for "family life" scale in SSA patients), indicating notable perceived functioning impairment. No socio-demographic factor was associated with the SDS distribution in any diagnostic group. However, in all patients, both SDS total scores and subscale scores directly correlated with a broad spectrum of clinical and psychopathological variables such as BDI, OASIS, MSI, and GSE (negative correlation) (data not shown). Associations with total SDS, revealed in linear regression analysis, were nonetheless fewer and showed less congruity (Table 3). Thus, BDI was the only one measure associated with SDS across all diagnostic groups. The OASIS had regression weight in SSA and BD groups, and GSE in SSA and DD groups. Older age was associated with functional impairment only in DD patients.

3.3. Objective work status

Overall, a high proportion of all patients had sick leave or disability pension (Table 4). Of all subjects with SSA, only 5.3% remained at work, while such figures for BD and DD groups were 29.3% and 33.0%, respectively. Gender, marital status, and educational level did not affect ability to work in any diagnostic group (data not shown). Older age was associated with work disability in the BD group ($P = 0.003$), and earlier age at onset in the SSA group ($P = 0.010$). Subjects of the SSA and BD groups with repeated hospitalizations ($P = 0.013$ and $P = 0.030$, respectively) and longer duration of treatment ($P = 0.003$ and $P = 0.014$,

Table 1
Socio-demographic and clinical characteristics of the sample.

	SSA		BD		DD		Total		*P*-value
	n	%	*n*	%	*n*	%	*n*	%	
Number	113	28.3	99	24.8	188	46.9	400	100.0	
Female	54	47.8	63	63.6	146	77.7	263	65.8	<0.001[a]
Marital status									<0.001[a]
Married/cohabitating	10	9.1	37	37.4	68	36.6	115	29.1	
Divorced/widowed	19	17.3	30	30.3	39	21.0	88	22.3	
Unmarried	81	73.6	32	32.3	79	42.4	192	48.6	
No children	97	89.0	58	59.8	130	70.7	285	73.1	<0.001[a]
Professional education	68	61.8	71	71.7	121	65.1	260	65.8	0.307[a]
AUD diagnosis	25	22.1	30	30.3	29	15.4	84	21.0	0.012[a]
Inpatients	36	31.9	20	20.2	34	18.1	102	22.8	0.018[a]
Age, mean (SD)	44.3 (12.4)		43.4 (12.3)		41.2 (13.3)		42.0 (13.0)		0.002[b]
Age at onset, mean (SD)	30.5 (12.3)		35.0 (12.7)		35.5 (14.0)		34.0 (13.4)		0.006[b]
Number of hospitalizations, mean (SD)	2.0 (1.1)		1.5 (1.3)		0.9 (1.2)		1.4 (1.3)		<0.001[b]
BDI, mean (SD)	18.0 (12.2)		22.3 (11.5)		27.7 (12.5)		23.6 (12.8)		<0.001[b]
OASIS, mean (SD)	9.4 (5.5)		10.8 (4.4)		11.0 (4.8)		10.5 (5.0)		0.040[b]
GSE, mean (SD)	21.7 (7.8)		21.2 (6.3)		19.1 (6.3)		20.4 (6.8)		0.006[b]
MSI, mean (SD)	5.2 (3.0)		6.0 (2.5)		5.4 (2.7)		5.5 (2.8)		0.131[b]

SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder; AUD: alcohol use disorder; BDI: Beck Depression Inventory; OASIS: Overall Anxiety Severity and Impairment Scale; GSE: General Self-Efficacy Scale; MSI: McLean Screening Instrument for borderline personality disorder.

[a] Chi^2 test.

[b] Kruskall–Wallis test (between-group comparison).

Table 2
Distribution of Sheehan Disability Scale scores by domains across diagnostic groups.

Mean (SD)	SSA ($n = 113$)	BD ($n = 99$)	DD ($n = 188$)	*P*-value
SDS summary	16.3 (7.7)	17.7 (7.9)	20.9 (7.6)	< 0.001[a]
Work	6.3 (3.2)	6.7 (3.3)	7.3 (3.0)	< 0.001[a]
Social life or leisure activities	5.5 (3.1)	5.7 (3.0)	6.9 (2.9)	< 0.001[a]
Family life or home responsibilities	4.4 (3.3)	5.3 (2.9)	6.4 (2.9)	0.019[a]

SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder; SDS: Sheehan Disability Scale.
[a] Kruskall–Wallis test.

Table 3
Linear regression analysis of clinical correlates for Sheehan Disability Scale within diagnostic groups.

	SSA ($n = 113$)			BD ($n = 99$)			DD ($n = 188$)		
	B	β	Sig.	B	β	Sig.	B	β	Sig.
Age	0.02	0.02	0.654	0.01	0.02	0.876	0.25	**0.44**	**0.004**
Age at onset	−0.04	−0.05	0.407	−0.03	−0.05	0.716	−0.15	−0.30	0.071
Number of hospitalizations	0.74	0.10	0.136	0.19	0.03	0.408	0.49	0.06	0.256
BDI	0.15	0.27	**0.026**	0.35	0.50	**0.000**	0.30	0.50	**0.000**
OASIS	0.40	0.34	**0.007**	0.44	0.24	**0.032**	0.15	0.12	0.196
GSE	−0.24	−0.26	**0.006**	−0.06	0.05	0.594	−0.20	−0.18	**0.010**
MSI	0.38	0.15	0.125	0.25	0.01	0.933	0.16	0.06	0.399
	$R^2 = 0.432$			$R^2 = 0.402$			$R^2 = 0.465$		

P-value at statistically significant level (< 0.05) is bolded. SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder; SDS: Sheehan Disability Scale, summary scores; BDI: Beck Depression Inventory; OASIS: Overall Anxiety Severity and Impairment Scale; GSE: General Self-Efficacy Scale; MSI: McLean Screening Instrument for borderline personality disorder; R^2: adjusted R square.

Table 4
Objective work status and subjective ability to work.

	SSA ($n = 113$)		BD ($n = 99$)		DD ($n = 188$)		*P*-value
	n	%	*n*	%	*n*	%	
Objective work status							
Working	6	5.3	29	29.3	62	33.0	< 0.001[a]
Sick leave	6	5.3	12	12.1	41	21.8	
Disability pension/rehabilitation subsidy	101	89.3	58	58.6	85	45.2	
Subjective ability to work							
Able to work	57	52.8	46	46.9	87	46.8	0.614[a]
Unable to work	51	47.2	52	53.1	99	53.2	
Correlation between objective and subjective work ability within groups (Spearman's rank)							
	$r = 0.09$	$P = 0.379$	$r = 0.58$	$P < 0.001$	$r = 0.55$	$P < 0.001$	

SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder.
[a] Chi^2 test (between diagnostic groups comparison).

respectively) were more often withdrawn from work than DD patients. BD patients with work disability showed higher SDS scores, and DD patients with work disability higher SDS, OASIS, and BDI scores and lower GSE scores than their able counterparts. No such associations emerged in the SSA group (data not shown), nor were any associations found for MSI in any group. Logistic regression analysis demonstrated direct associations of work disability with SDS and number of hospitalizations in all groups and an inverse association with GSE in the SSA group (Table 5). In addition, age and age at onset had regression weight in the BD group. The results remained the same when SDS was excluded from the model.

3.4. Subjective ability to work

Near half of the patients of all groups reported work disability (Table 4). Perceived work disability was related to older age in SSA and DD groups ($P = 0.001$ and $P = 0.004$, respectively) and to number of hospitalizations in the BD group ($P = 0.036$). No associations emerged regarding other socio-demographic and background characteristics (data not shown). Patients with perceived work disability of all groups scored higher in OASIS, BDI, and SDS and lower in GSE, and only in the DD group had higher MSI scores than their able to work counterparts (data not shown). Logistic regression analysis revealed less consistent associations (Table 5). Thus, SDS had regression weight in BD and DD groups, and BDI in all groups. The exclusion of SDS from this model did not change the results. The MSI dropped from the final regression model because of its insignificance in SSA and BD groups.

3.5. Objective work status vs. subjective work ability

The proportions of patients working and subjectively able to work correlated moderately strongly and significantly among BD and DD patients ($P < 0.001$), but not in the SSA group ($P = 0.379$).

4. Discussion

This study investigated level of functioning plus subjective and objective ability to work among psychiatric care patients. Most of the patients, irrespective of diagnosis, reported marked functional impairment. Of all diagnostic groups, subjects with schizophrenia or schizoaffective disorder were mostly outside the labour force, but concurrently subjectively experienced the least functional difficulties. In contrast, among patients with mood disorders, objective and subjective indicators for ability to work were broadly

Table 5
Multivariate logistic regression analysis of clinical correlates for objective and subjective ability to work within diagnostic groups.

	SSA ($n = 113$)		BD ($n = 99$)		DD ($n = 188$)	
	B	Sig.	B	Sig.	B	Sig.
Objective work status[a]						
Age	0.03	0.623	0.28	**0.002**	0.05	0.238
Age at onset	−0.30	0.155	−0.21	**0.009**	−0.06	0.120
Number of hospitalizations	2.06	**0.019**	0.77	**0.005**	0.43	**0.013**
BDI	0.01	0.906	0.04	0.461	0.03	0.172
OASIS	0.25	0.451	0.04	0.700	0.06	0.288
GSE	−0.36	**0.026**	−0.08	0.198	0.02	0.578
SDS (except "work" item)	0.43	**0.031**	0.17	**0.005**	0.14	**0.000**
Subjective ability to work[b]						
Age	0.05	**0.037**	0.02	0.560	0.03	0.399
Age at onset	−0.01	0.698	0.02	0.622	0.05	0.130
Number of hospitalizations	0.14	0.516	0.82	**0.009**	0.16	0.329
BDI	0.09	**0.005**	0.13	**0.023**	0.10	**0.000**
OASIS	0.03	0.657	0.11	0.300	0.08	0.144
GSE	−0.01	0.838	−0.07	0.232	−0.06	0.165
SDS (except "work" item)	0.07	0.121	0.23	**0.002**	0.22	**0.000**

P-value at statistically significant level (< 0.05) is bolded. SSA: schizophrenia or schizoaffective disorder; BD: bipolar disorder; DD: depressive disorder; BDI: Beck Depression Inventory; OASIS: Overall Anxiety Severity and Impairment Scale; GSE: General Self-Efficacy Scale; SDS: Sheehan Disability Scale ("work" item excluded).
[a] Information on work status collected from medical records/certificates by authors.
[b] Patients' perceived ability to work.

convergent. Within all groups, current depressive symptoms contributed to self-reported impairment, while recurrent psychiatric hospitalizations were associated with objective work status.

4.1. Self-reported functional impairment

Perceived level of functioning, as measured by the Sheehan Disability Scale, was clearly deteriorated in all diagnostic groups. However, somewhat unexpectedly, the most subjectively impaired group across all three domains was the unipolar depressive patients. Unlike our study, most previous studies conducted in psychiatric settings have compared disability only between two major mental disorders. Wide variations in observed functioning have been reported. For instance, van der Voort et al. [46] found more prominent functional impairment in BD patients than in DD patients. Bowie et al. [30] and Simonsen et al. [47] reported more severe disability in schizophrenia than in BD. In contrast, Lee et al. [31], in comparing patients with DD, BD, or psychosis, did not find the principal diagnosis of mental disorder to be a significant predictor of functional outcome, which was instead predicted by neuropsychological functioning. However, the same group in further work found more favourable vocational prognosis for patients with BD rather than DD or schizophrenia spectrum disorder [29].

Correlates of perceived disability could conceivably differ markedly between the major mental disorders. However, we found that depressive symptoms consistently appeared as the major contributor to perceived impairment not only in DD and BD but also in SSA. Depressive symptoms are essential for poor psychosocial functioning in mood disorders [26,46,48–50] overall, but the negative bias in self-referential thinking in depression [51] may be of particular importance for an exaggeratedly negative view of perceived level of functioning. Thus, finding DD patients to report the highest subjective functional impairment of all groups is, perhaps, not surprising, as they experienced the most severe depressive symptoms (BDI) as well. In schizophrenia spectrum disorders, affective symptoms impair functioning as a secondary condition; in part, some negative symptoms, such as anhedonia, may overlap with those of depression [52–55]. Overall, our finding of depressive and, to some extent, anxiety symptoms contributing to functional impairment highlights the importance of measuring them when assessing level of functioning.

4.2. Work status

Differences in work status between the diagnostic groups were notable. Only few (5.3%) of our SSA patients were working, in contrast to nearly half of the mood disorder patients. Despite DD patients reporting the highest level of functional impairment on the SDS, they were still the most employed group of all. Such a discrepancy could refer to overall subjective underestimation of functional capacity by patients with depression compared with objective assessment [18,19,22]. Regression analyses indicated the association of numbers of hospitalizations with current labour status as unemployed, pensioned, or being on sick leave. Previous studies also demonstrate that preceding course of disease (i.e. duration of illness and hospitalizations required) is strongly related to subsequent job loss due to disability pension in schizophrenia spectrum disorders [53,56], bipolar disorder [24], and depression [23,27]. We assume that number of hospitalizations represents a proxy for the overall severity, duration, chronicity, and recurrent course of the principal mental disorder, which jointly will commonly lead to disability pension. Another major correlate of long-term work disability or pensioning across all diagnostic groups was the perceived functional impairment as measured by the SDS. The studies on this topic vary by methodology and functioning assessment tools. Nevertheless, poor self-rated functioning is likely to predict negative outcome of employment in all mental disorders [23,24,57–59]. However, regardless of the primary psychopathology, our findings highlight the importance of overall level of functioning for retaining occupational roles. Work status was correlated not only specifically with perceived disability at work but also with functioning in other areas of life. Thus, in all three diagnostic groups, both poor overall functioning and the factors jointly resulting in repeated hospitalizations were the strongest correlates for poor work status.

4.3. Objective work status vs. subjective work ability

In terms of perceived work disability, the most significant finding was a marked gap between actual labour status and subjective work ability in the SSA group. While again only 5.3% of these patients remained employed, concurrently half of them perceived themselves as able to work. Such findings are in accordance with the general phenomenon of discordance between self-reporting and assessor-rating in SSA patients. Previous studies

have indicated that, due to low insight and neurocognitive and, to some extent, negative symptoms, patients with schizophrenia spectrum disorder tend to markedly overestimate their functional level [21,22] and overall quality of life [60,61] comparing to the evaluation of a clinician. Additionally, our result of high-perceived work ability in SSA patients could partially reflect the finding that subjects with severe mental illness (i.e. schizophrenia spectrum disorders) still strongly desire to work [25]. However, it is possible that besides poor insight particularly long-term SSA patients outside working life may have a different frame of reference for judging their functioning. Because of such a discordance, clinicians should evaluate functioning of SSA patients comprehensively, including both subjective and objective aspects [62]. Their work status is likely not only related to their illness, but also dependent on context (social support, health care system, rehabilitation, etc.). Furthermore, low employment in the SSA group raises the issue of need for more effective employment programs for such patients.

Contrary to the SSA group, perceived and actual work ability were moderately strongly correlated in our mood disorder patients. Their level of self-reported work ability was, nevertheless, slightly higher than their vocational status. Such a disproportion could result from delayed functional recovery compared with syndromal remission [46]. Thus, relief of symptoms is likely to enhance subjective but not objective ability to work.

The correlates of perceived work ability were roughly akin to those of self-reported functional impairment. The most consistent finding across all groups was the association of subjective work disability with current depressive symptoms. Thus, clinicians should pay attention to carefully uncovering and effectively treating affective symptoms regardless of their psychopathological domain to improve the patient's engagement in rehabilitation programmes and eventually expedite their return to work.

4.4. Study strengths and limitations

Strengths of this study include investigation of reported functioning, perceived ability to work, and work status along with clinical characteristics simultaneously across diagnostically heterogeneous (schizophrenia or schizoaffective disorder, bipolar disorder, and depression) psychiatric care patients in the Helsinki metropolitan area. This allowed comparison of the diagnostic groups in terms of the measures of functioning, their correlates, and the consistency of objective and subjective measures.

Our study also has several limitations. First, all results for the SSA group should be interpreted with caution due to the low number ($n = 6$) of subjects remaining at work, and thus, the low statistic power in some bivariate and multivariate analyses. Second, as this study, which included a long survey, was performed in a busy routine clinical practice, the response rate was only 33%. However, according to register-based analysis of representativeness, our sample did not differ from the patient populations of participating organizations in terms of gender or age. Regarding demographic characteristics, our study is comparable with the earlier screening-based Vantaa Depression Study and Jorvi Bipolar Study [63,64], but the proportion of patients with disability pension was 18–19% higher in this study [23,24]. Third, the generalizability of the findings of this Helsinki metropolitan area study (also considering relatively low response rate) to other settings needs to be verified. Fourth, principal clinical diagnoses were set in psychiatric care by psychiatrists and residents (although not always based on structured interviews), and in addition verified by the authors from available medical records. Additionally, we did not use any clinician-rated work ability measures and utilized only data on employment status as an objective measure of work ability. The information on employment status was collected only from medical records and was not corroborated from the Finnish Social Insurance Institution or other registers. Fifth, because this was a cross-sectional study, no firm conclusions can be made on causal relationships between demographic or clinical variables and level of functioning or work ability. Sixth, recall bias could affect self-report measures, and some patients could under- or overestimate their symptoms, both factors bias our analyses. Seventh, the study included multiple descriptive statistical analyses, which increases risk of spurious findings. However, we used multivariate regression models to test our hypotheses on risk factors of functional impairment and work disability. Eighth, cognitive functioning is a highly relevant factor influencing functional outcome, but could not be assessed in this study.

5. Conclusions

Psychiatric care patients commonly suffer from marked disability and eventually end up outside the labour force. However, while among patients with mood disorders objective and subjective indicators of ability to work are largely concordant, among those with schizophrenia or schizoaffective disorder they are commonly contradictory. Among all groups, perceived functional impairment and work disability are coloured by current depressive symptoms. In contrast, objective work status reflects illness course, particularly number of preceding psychiatric hospitalizations.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1545–602.
[2] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2163–96.
[3] Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PLoS One 2015;10(2):e0116820.
[4] Mojtabai R, Stuart EA, Hwang I, Susukida R, Eaton WW, Sampson N, et al. Long-term effects of mental disorders on employment in the National Comorbidity Survey ten-year follow-up. Soc Psychiatry Psychiatr Epidemiol 2015;50(11):1657–68.
[5] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2197–223.
[6] Laaksonen M, Gould R. Return to work after temporary disability pension in Finland. J Occup Rehabil 2015;25(3):471–80.
[7] Ekberg K, Wahlin C, Persson J, Bernfort L, Oberg B. Early and late return to work after sick leave: predictors in a cohort of sick-listed individuals with common mental disorders. J Occup Rehabil 2015;25(3):627–37.
[8] Netterstrom B, Eller NH, Borritz M. Prognostic factors of returning to work after sick leave due to work-related common mental disorders: a one- and three-year follow-up study. Biomed Res Int 2015;596572. http://dx.doi.org/10.1155/2015/596572 [Epub 2015 Oct 18].
[9] Lahelma E, Pietilainen O, Rahkonen O, Lallukka T. Common mental disorders and cause-specific disability retirement. Occup Environ Med 2015;72(3):181–7.
[10] Kaila-Kangas L, Haukka E, Miranda H, Kivekas T, Ahola K, Luukkonen R, et al. Common mental and musculoskeletal disorders as predictors of disability retirement among Finns. J Affect Disord 2014;165:38–44.
[11] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367(9524):1747–57.
[12] Chen FP, Samet S, Gorroochurn P, O'Hara KM. Characterizing factors of employment status in persons with major depressive disorder. Eval Health Prof 2016;39(3):263–81.
[13] Marwaha S, Durrani A, Singh S. Employment outcomes in people with bipolar disorder: a systematic review. Acta Psychiatr Scand 2013;128(3):179–93.

[14] Goldberg JF, Harrow M. A 15-year prospective follow-up of bipolar affective disorders: comparisons with unipolar nonpsychotic depression. Bipolar Disord 2011;13(2):155–63.
[15] Miettunen J, Lauronen E, Veijola J, Koponen H, Saarento O, Taanila A, et al. Socio-demographic and clinical predictors of occupational status in schizophrenic psychoses – follow-up within the Northern Finland 1966 Birth Cohort. Psychiatry Res 2007;150(3):217–25.
[16] Marwaha S, Johnson S. Schizophrenia and employment – a review. Soc Psychiatry Psychiatr Epidemiol 2004;39(5):337–49.
[17] Rosenheck R, Leslie D, Keefe R, McEvoy J, Swartz M, Perkins D, et al. Barriers to employment for people with schizophrenia. Am J Psychiatry 2006;163(3):411–7.
[18] Pranjic N, Males-Bilic L. Work ability index, absenteeism and depression among patients with burnout syndrome. Mater Sociomed 2014;26(4):249–52.
[19] Zimmerman M, Martinez JA, Attiullah N, Friedman M, Toba C, Boerescu DA, et al. Why do some depressed outpatients who are in remission according to the Hamilton Depression Rating Scale not consider themselves to be in remission? J Clin Psychiatry 2012;73(6):790–5 [Physicians Postgraduate Press, Inc.].
[20] Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E. Functional impairment in the remission phase of bipolar disorder. Bipolar Disord 2005;7(3):281–5.
[21] Oorschot M, Lataster T, Thewissen V, Lardinois M, van Os J, Delespaul PA, et al. Symptomatic remission in psychosis and real-life functioning. Br J Psychiatry 2012;201(3):215–20.
[22] Huppert JD, Weiss KA, Lim R, Pratt S, Smith TE. Quality of life in schizophrenia: contributions of anxiety and depression. Schizophr Res 2001;51(2–3):171–80.
[23] Holma IA, Holma KM, Melartin TK, Rytsala HJ, Isometsa ET. A 5-year prospective study of predictors for disability pension among patients with major depressive disorder. Acta Psychiatr Scand 2012;125(4):325–34.
[24] Arvilommi P, Suominen K, Mantere O, Valtonen H, Leppamaki S, Isometsa E. Predictors of long-term work disability among patients with type I and II bipolar disorder: a prospective 18-month follow-up study. Bipolar Disord 2015;17(8):821–35.
[25] Tsang HW, Leung AY, Chung RC, Bell M, Cheung WM. Review on vocational predictors: a systematic review of predictors of vocational outcomes among individuals with schizophrenia: an update since 1998. Aust N Z J Psychiatry 2010;44(6):495–504.
[26] Gutierrez-Rojas L, Jurado D, Gurpegui M. Factors associated with work, social life and family life disability in bipolar disorder patients. Psychiatry Res 2011;186(2–3):254–60.
[27] Rytsälä HJ, Melartin TK, Leskela US, Sokero TP, Lestela-Mielonen PS, Isometsa ET. Predictors of long-term work disability in Major Depressive Disorder: a prospective study. Acta Psychiatr Scand 2007;115(3):206–13.
[28] Braga RJ, Mendlowicz MV, Marrocos RP, Figueira IL. Anxiety disorders in outpatients with schizophrenia: prevalence and impact on the subjective quality of life. J Psychiatr Res 2005;39(4):409–14.
[29] Lee RS, Hermens DF, Naismith SL, Lagopoulos J, Jones A, Scott J, et al. Neuropsychological and functional outcomes in recent-onset major depression, bipolar disorder and schizophrenia spectrum disorders: a longitudinal cohort study. Transl Psychiatry 2015;5:e555.
[30] Bowie CR, Depp C, McGrath JA, Wolyniec P, Mausbach BT, Thornquist MH, et al. Prediction of real-world functional disability in chronic mental disorders: a comparison of schizophrenia and bipolar disorder. Am J Psychiatry 2010;167(9):1116–24.
[31] Lee RS, Hermens DF, Redoblado-Hodge MA, Naismith SL, Porter MA, Kaur M, et al. Neuropsychological and socio-occupational functioning in young psychiatric outpatients: a longitudinal investigation. PLoS One 2013;8(3):e58176.
[32] Bahorik AL, Eack SM. Examining the course and outcome of individuals diagnosed with schizophrenia and comorbid borderline personality disorder. Schizophr Res 2010;124(1–3):29–35.
[33] Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Sustained unemployment in psychiatric outpatients with bipolar depression compared to major depressive disorder with comorbid borderline personality disorder. Bipolar Disord 2012;14(8):856–62.
[34] Cardenas V, Abel S, Bowie CR, Tiznado D, Depp CA, Patterson TL, et al. When functional capacity and real-world functioning converge: the role of self-efficacy. Schizophr Bull 2013;39(4):908–16.
[35] Norman SB, Cissell SH, Means-Christensen AJ, Stein MB. Development and validation of an Overall Anxiety Severity and Impairment Scale (OASIS). Depress Anxiety 2006;23(4):245–9.
[36] Baryshnikov I, Aaltonen K, Koivisto M, Näätänen P, Karpov B, Melartin T, et al. Differences and overlap in self-reported symptoms of bipolar disorder and borderline personality disorder. Eur Psychiatry 2015;30(8):914–9.
[37] Aaltonen K, Näätänen P, Heikkinen M, Koivisto M, Baryshnikov I, Karpov B, et al. Differences and similarities of risk factors for suicidal ideation and attempts among patients with depressive or bipolar disorders. J Affect Disord 2016;193:318–30.
[38] Karpov B, Joffe G, Aaltonen K, Suvisaari J, Baryshnikov I, Näätänen P, et al. Anxiety symptoms in a major mood and schizophrenia spectrum disorders. Eur Psychiatry 2016;37:1–7.
[39] World Health Organization. International classification of disease, 10th ed., Geneva: WHO; 1992.
[40] Sheehan DV. The anxiety disease. New York, NY, USA: Charles Scribners Sons; 1983.
[41] Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11(Suppl. 3):89–95.
[42] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
[43] Schwarzer R, Jerusalem M. Generalized Self-Efficacy Scale. In: Weinman J, Wright S, Johnston M (eds.). Measures in health psychology: a user's portfolio. Causal and control beliefs. Windsor, UK: NFER-NELSON; 1995. p. 35–37.
[44] Zanarini MC, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J. A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). J Pers Disord 2003;17(6):568–73.
[45] IBM SPSS Statistics for Windows, Version 22.0. Released 2013. Armonk, NY: IBM Corp; 2005.
[46] van der Voort TY, Seldenrijk A, van Meijel B, Goossens PJ, Beekman AT, Penninx BW, et al. Functional versus syndromal recovery in patients with major depressive disorder and bipolar disorder. J Clin Psychiatry 2015;76(6):e809–14 [Physicians Postgraduate Press, Inc, United State].
[47] Simonsen C, Sundet K, Vaskinn A, Ueland T, Romm KL, Hellvin T, et al. Psychosocial function in schizophrenia and bipolar disorder: relationship to neurocognition and clinical symptoms. J Int Neuropsychol Soc 2010;16(5):771–83 [England].
[48] Hendriks SM, Spijker J, Licht CM, Hardeveld F, de Graaf R, Batelaan NM, et al. Long-term work disability and absenteeism in anxiety and depressive disorders. J Affect Disord 2015;178:121–30.
[49] Rosa AR, Franco C, Martinez-Aran A, Sanchez-Moreno J, Reinares M, Salamero M, et al. Functional impairment in patients with remitted bipolar disorder. Psychother Psychosom 2008;77(6):390–2.
[50] Goldberg JF, Harrow M. A 15-year prospective follow-up of bipolar affective disorders: comparisons with unipolar nonpsychotic depression. Bipolar Disord 2011;13(29):155–63.
[51] Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci 2011;12(8):467–77.
[52] Sönmez N, Rossberg JI, Evensen J, Barder HE, Haahr U, Ten Velden Hegelstad W, et al. Depressive symptoms in first-episode psychosis: a 10-year follow-up study. Early Interv Psychiatry 2016;10(3):227–33.
[53] Johnson S, Sathyaseelan M, Charles H, Jacob KS. Predictors of disability: a 5-year cohort study of first-episode schizophrenia. Asian J Psychiatr 2014;9:45–50.
[54] Harvey PD. Disability in schizophrenia: contributing factors and validated assessments. J Clin Psychiatry 2014;75(Suppl. 1):15–20.
[55] Braga RJ, Reynolds GP, Siris SG. Anxiety comorbidity in schizophrenia. Psychiatry Res 2013;210(1):1–7.
[56] Alptekin K, Erkoc S, Gogus AK, Kultur S, Mete L, Ucok A, et al. Disability in schizophrenia: clinical correlates and prediction over 1-year follow-up. Psychiatry Res 2005;135(2):103–11.
[57] Razzano LA, Cook JA, Burke-Miller JK, Mueser KT, Pickett-Schenk SA, Grey DD, et al. Clinical factors associated with employment among people with severe mental illness: findings from the employment intervention demonstration program. J Nerv Ment Dis 2005;193(11):705–13.
[58] Catty J, Lissouba P, White S, Becker T, Drake RE, Fioritti A, et al. Predictors of employment for people with severe mental illness: results of an international six-centre randomised controlled trial. Br J Psychiatry 2008;192(3):224–31.
[59] Depp CA, Mausbach BT, Bowie C, Wolyniec P, Thornquist MH, Luke JR, et al. Determinants of occupational and residential functioning in bipolar disorder. J Affect Disord 2012;136(3):812–8.
[60] Hayhurst KP, Massie JA, Dunn G, Lewis SW, Drake RJ. Validity of subjective versus objective quality of life assessment in people with schizophrenia. BMC Psychiatry 2014;14 [365-014-0365-x].
[61] Bengtsson-Tops A, Hansson L, Sandlund M, Bjarnason O, Korkeila J, Merinder L, et al. Subjective versus interviewer assessment of global quality of life among persons with schizophrenia living in the community: a Nordic multicentre study. Qual Life Res 2005;14(1):221–9.
[62] Harvey PD. Assessing disability in schizophrenia: tools and contributors. J Clin Psychiatry 2014;75(10):e27.
[63] Mantere O, Suominen K, Leppämäki S, Valtonen H, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). Bipolar Disord 2004;6(5):395–405.
[64] Melartin TK, Rytsala HJ, Leskela US, Lestela-Mielonen PS, Sokero TP, Isometsa ET. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. J Clin Psychiatry 2002;63(2):126–34.